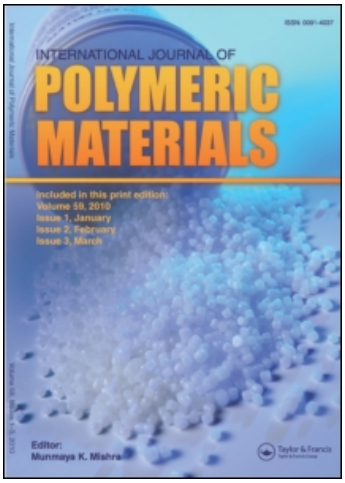

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Quantitative Foundations of Polymer Biocompatibility and Biodestructibility

K. Z. Gumargalieva[a]; G. E. Zaikov[a]; Yu. V. Moiseev[a]
[a] Institute of Chemical Physics, Academy of Sciences of Russia, Moscow

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Quantitative Foundations of Polymer Biocompatibility and Biodestructibility

K. Z. GUMARGALIEVA, G. E. ZAIKOV and YU. V. MOISEEV

Institute of Chemical Physics, Academy of Sciences of Russia, Moscow, Russia

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The quantitative aspects of degradation of some polymer used in medical practice as surgical implants are reviewed. The quantitative criteria of biocompatibility of these polymers and their response to the living body are discussed. New experimental data are shown relating the degradation rate of polyesters, polyamides, elastomers in the organism to that in model media. The catalytical activity of biological media (water, salts and enzymes) are also considered in detail.

KEY WORDS Implants (surgical), biocompatibility, biodegradation, degradation, polyesters, polyamides, polydimethylsiloxane, polyurethanes, polyolefines.

1. INTRODUCTION

Polymers are used in almost any field of medicine. They are widely used in restorative surgery as prosthesis, coverings for wounds and burns, blood substitutes, packaging for drugs, medical equipment parts, etc.

Two basic questions are of interest to the bioengineer producing the items and the physician using them in practice. Namely, their biocompatibility and the retaining of their effective mechanical, diffusive, optical and other properties.

On contact with biologically active media, such as blood, drugs and so on, most polymers undergo two interrelated processes, the degradation of polymers under the action of biologically active substances and interaction of the polymer degradation products with the biological medium.

A quantitative characterization of the biocompatibility and biodegradation of polymers used in medicine is the objective of the present work.

2. BODY RESPONSE TO A POLYMER

A polymer contacting the tissues of a living body, changes its own chemical and physical properties, but being foreign to the body it also induces specific responses to the latter.

2.1 Initial Response

Implantation of polymers in a living body results in inflammatory response caused by tissue damage.[1] At the initial stage, the following takes places in the damage zone: a decrease in pO_2-partial pressure blood saturation and pH; a decrease in potassium, sodium, calcium and magnium ion concentration; an accumulation of physiologically active substances caused by degradation of cell membranes and discharge from circulating lymphocytes; and an increase in permeability. At the second stage, a chemotaxis (directed motion of cells attracted to the inflammation zone by chemical irritants) results in accumulation of various kinds of cells (neutrophils, monocytes, basophils, macrophages, etc.). The chemical irritants are physiologically active substances discharged by damaged cells and tissues, and also substances yielded by polymer materials (degradation products, catalyst residues, stabilisers, fillers, and so on).[1,2]

Thus, at the second stage, polymer materials may affect the course of the inflammatory response depending on the kind and site of operation. This stage of the inflammatory reaction usually terminates in three days due to substitution of the neutrophils by monocytes, lymphocytes, macrophages and plasma cells.[3]

2.2 Forming of Capsule on Polymer Surface

In four or five days after operation, macrophages predominate near the polymer; however, lymphocytes, plasma cells, and fibroblasts are also quite abundant.[4]

If the polymer is biocompatible, in 1–2 weeks the macrophage population becomes markedly lower, and fibroblasts form a collagenous capsule on the polymer surface.[5] If the polymer biocompatibility is low, the macrophages may remain near the implanted polymer for a longer time, frequently forming giant cells. The capsule sizes vary from 0.05 to 1.5 mm depending on the polymer biocompatibility.[6] If the inflammatory agent, e.g., the degradation product is discharged steadily, this results in a chronic inflammation, which continues for a long time till complete degradation of the polymer.

Macrophages as the basic phagocytary cells in the living body take an active part in the degradation of most polymers. Macrophages contain lysosomes, which act as the "digestive tract of a cell."[7] Lysosomal enzymes, chiefly hydrolases, may degrade polymers through phagocytosis. Salthouse[3] shows a macrophage lysosomal system and two phagocytotic pathways: (1) Exocytosis, when lysosomal enzymes leave the macrophage, and degradation occurs on the polymer surface; and (2) endocytosis, when intracell degradation is preceded by macrophages.

Winter,[8] for instance, detected metal particles in the macrophages by the spectroscopy technique.

The dynamics of morphological changes occurring on the polymer surface after implantation is presented in Figure 1.

3. BIOCOMPATIBILITY

The problem of polymer biocompatibility will now be considered.

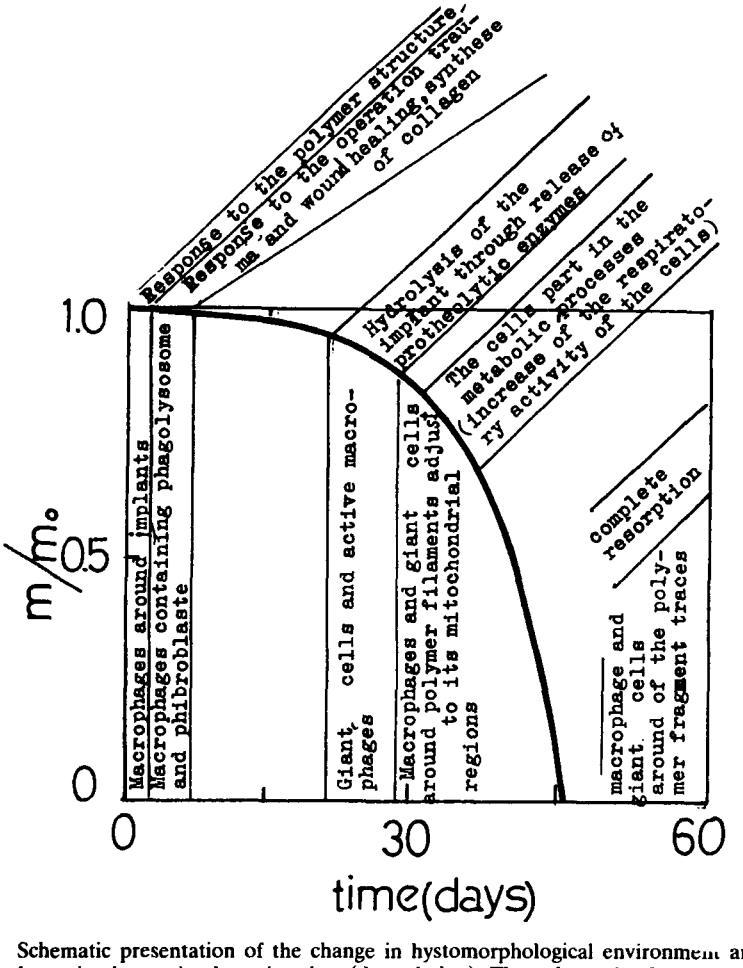


FIGURE 1 Schematic presentation of the change in hystomorphological environment around biocompatible polymer implant vs implantation time (degradation). The polymer implant is an absorbable suture from polyglycolide.

3.1 General Definitions

Polymers implanted in the living body must ensure special prosthetic functions or be used for diagnostic, surgical and therapeutic purposes without injuring the surrounding tissues and the living body as a whole. There is so far no clear and short definition of biocompatibility, since there are no specific materials, parameters or biological tests that would permit quantitative definition of this property.[9]

Biocompatibility means that the polymer must not damage blood cells, and enzymes; and must not cause thrombus formation, tissue degradation, harmful toxic, and allergic responses.

Pure polymers of a high molecular mass generally display low toxicity.[10] Macromolecular degradation results in fragments of a lower molecular mass, monomers are formed in specific cases. The toxicity of polymers of the same homologous series is known to be inversely proportional to the molecular mass.[10]

The biocompatibility of the material varies depending on the rate of biological medium degradation by the implant.

The biocompatibility of a polymer material depends not only on its initial properties, but also on its chemical stability to the surrounding biological medium.

3.2 Techniques for Determining Biocompatibility

A series of publications describing the attempts to test polymers for biocompatibility was published in the recent years.[11-14]

The tissue culture screening, which consists in growing cells on the surface of a test material is generally used in vitro. Two versions of this technique are known: (a) spraying the polymer with an agar-agar layer and subsequently observing cell reproduction in the medium; (b) spraying the polymer with cell, most frequently fibroblasts, with subsequent submerging of the cell-inoculated polymer in a culture medium.

As a rule, the effect of the polymer is studied for three cell functions: attachment, viability, and division.

Eleven microscopically observed events were observed here. Table I shows the polymer studied, the phenomena observed and value of the fibroblast cell population doubling (P.D.) parameter. P.D. is defined by equation:

$$\text{P.D.} = (\ln N/N_0)/0.69 \tag{1}$$

where N is the number of cells after 48 hr incubation; and N_0 the initial number of viable cells inoculated to the polymer.

TABLE I

Polymer cytotoxicity: Microscopic observations

Polymer	Observations	P.D.	Class of toxicity
Poly(propiolactone)	1	2.7	1
Teflon	1	2.1	1
Polylactic acid	1	1.6	1
Poly(ethylene oxide)	1	2.1	1
Poly(acrylamide)	1	2.0	1
Poly(caprolactone)	1	2.1	1
Polyacrylonitrile	1	2.1	1
Poly(glycolic acid)	1	2.0	1
Poly(methyl methacrylate)	1, 11	—	11
Poly(methyl L(+)lactyl 2-cyanoacrylate	7, 8, 10	—	11
Poly(1,2-isopropylidene glycerol cyanoacrylate)	4	0.4	11
Poly(isobutyl-2-cyanoacrylate)	1	2.0	11
Poly(1,2-isopropylidene glycerol cyanoacrylate) low M.M.	2, 5, 6, 7	—	111
Poly(acrylic acid)	5, 8, 9	—	111
Poly(methyl-2-cyanoacrylate)	5, 7, 8	—	111

Observations: 1—Normal cell attachment to normal growing cells throughout a 48 hr test period; 2—A few cells attached initially; 3—The few cells attached appeared to grow normally; 4—Few cells attached after 48 hr; 5—All cells in medium dead; 6—All cells attached to growing surface after 48 hr; 7—Cell clumping; 8—No cells attached to growthing surface; 9—Had a sudden pH change to 5.2; 10—Had several variable cells in medium after 48 hr; 11—Polymer adhered to cells.

TABLE II

Polymer toxicity (in vivo)

	MSTS	Toxicity class
Gelatin	2.1	1
Polyacryloamide	10.3	1
Polyglycolide	19.6	1
Polyacrylonitrile	52.0	1
Poly-α-lactide	34.7	1
Poly-β-propiolactone	69.1	1
Polycaprolactone	37.3	1
Polyethyleneoxide	21.8	1
Polymethyl-α-lactylcyanoacrylate	56.7	11
Polymethyl-2-cyanoacrylate	59.1	111
Polyisobutyl-2-cyanoacrylate	49.7	111
Polymethylmethacrylate	49.2	111

On basis of the in vitro data, all the polymers were classified into three conventional toxicity groups (Table II).

The following six biocompatibility tests were performed in vivo: (a) extent of cell damage; (b) capsule thickness (total thickness of reaction); (c) number of polymorphonuclear leucocytes and erythrocytes; (d) overall cell number; (e) number of eosinophils, lymphocytes and giant cells; (f) number of fibrocytes and mononuclear phagocytes.

The amount of cells is normally determined microscopically over a standard area.

An eight-mark gradation has been used[13] for each test. The averaged factor (MSTS-mean standard toxicity score) for all the tests was found by adding the data for two implantation periods:

$$\text{MSTS} = \frac{(7 \text{ days STS}) + (28 \text{ days STS})}{10} \tag{2}$$

where STS (standard tissue score) is the averaged mark total for six tests.

Table II shows the MSTS values for various polymers after subcutaneous implantation in rats and conventional classification by toxicity.

Nichols[14] gives data of the capsule thickness relative to the degree of toxicity of two polymers.

4. DEGRADATION MACROKINETICS

Polymer degradation is generally understood to be the totality of chemical processes leading to changes in polymer chemical structure. These processes involve breaking of chemical bonds and are accompanied by changes in the polymer molecular mass.

The following macromolecular transformations can take place during degradation in biological media: (a) degradation of the main macromolecule chain resulting in a lower degree of polymerization; (b) conversion of atom groups within the mac-

romolecule, the initial extent of polymerization (polymer-analogous reactions) being retained; (c) depolymerization involving splitting of monomer molecules from the macromolecule end; (d) cross-linking accompanied by formation of chemical bonds between macromolecules.

Polymer degradation in biological media is a complex physico-chemical process involving diffusion of environmental components through the polymer and transformation of chemically weak bonds.

Depending on the ratio of the diffusion rate to the chemical reaction rate, the degradation may occur in different regions.

If the medium diffusion rate is commensurable with the chemical reaction rate; the reaction occurs in a given reaction zone, the size of which increases with time and reaches the polymer implant size. Here, the reaction occurs in the internal diffusive-kinetic region.

If the medium diffusion rate considerably exceeds the chemical reaction rate, after the medium becomes dissolved in the polymer, the degradation spreads over the entire polymer bulk, i.e. over the internal kinetic region.

If the medium diffusion rate considerably lower than the chemical reaction rate, the degradation takes place in a very thin reaction surface layer on the surface of the polymer implant, namely, in the external diffusive-kinetic region.

4.1 Internal Diffusive-Kinetic Region

The equation for the degradation rate of chemically unstable bonds in a polymer product is:

$$W = \frac{dC_n}{dt} = K(C_n^0 - C_n)C_{cat} \tag{3}$$

where C_n^0 is the initial concentration of chemically weak bonds in the polymer; C_n the concentration of broken bonds in the polymer; C_{cat} the catalyst concentration in the polymer.

The catalyst concentration in the polymer, for example of water, salt or enzymes, may be found from the equation:

$$\frac{dC_{cat}}{dt} = D_{cat}\nabla^2 C_{cat} - \sum_i C_{cat}C_i K_i \tag{4}$$

where ∇ is the Laplace operator; C_i the concentration of polymer functional groups capable of entering a complexing or substitution reaction; and K_i stands for constants of complex-formation or substitution reaction rates.

The second term in the right-hand side of Equation (4) accounts for the possibility of reactions such as protonation or complex formation involving functional groups and enzymes.

The following assumptions are commonly made:

(a) The polymer-catalyst system is, as a rule, diluted with respect to the catalyst, i.e. it can be taken as independent of the catalyst concentration in the polymer.

(b) The value of K is a constant; this is correct for a low medium solubility in the polymer.

(c) With this type of degradation, the implant loses its strength, even at low transformation levels, i.e. in some cases the condition $C_n^0 \sim C_n \approx C_n^0$ would be justified.

For simultaneous solution of Equations (3) and (4) the following boundary conditions are usually accepted:

(a) The concentration of diffusing substances on the implant surface is constant (this condition exists when the blood flow with constant concentration of catalytically active substances rapidly washes the implant).

(b) The concentration of diffusing substances on the implant surface is a time function during the inflammatory processes near the polymer.

To the first approximation, most polymer implants may be regarded as geometrical bodies.

The parallelepiped, cylinder, etc. are models of polymer membranes and coverings.

The solutions of Equations (3) and (4) for a parallelepiped and cylinder will be discussed below. Even under the above assumptions, the simultaneous solution of equations (3) and (4) is difficult.[20]

Here, we shall cite solutions for two cases only. $K_1 \to \infty$ i.e. the functional groups in the polymer formed in the course of degradation react with the catalyst practically irreversibly.

For the film of thickness l:

$$C_n = K_{obs} C_{cat}^0 t \cdot \left\{ 1 - \sum_{m=0}^{\infty} \frac{K_{obs} t (b_m^2 D_{cat} + K_{obs}) + b_m - D_{cat}^2 [1 - \exp - (b_m^2 D_{cat}^0 + K_{obs}) t]}{(2m + 1) b_m (b_m^2 D_{cat} + k_{obs})^2 l t} \right\} \tag{5}$$

where $b_m = (2m + 1)/l$; and C_{cat}^0 is the catalyst solubility in the polymer. When $D_{cat}^2 > K_{obs}$ only the first member can be retained.

For filament of radius r:

$$C_n = K_{obs} C_{cat}^0 \sum_{n=1}^{\infty} \frac{D_{cat} \mu_n^2}{r^2 z} \left[t - \frac{1 - \exp(zt)}{z} \right] \tag{6}$$

where $z = D_{cat} \mu_n^2 / r^2 + K_{obs}$, and μ_n are roots of the Bessel function.

When $D_{cat} \mu_n^2 / r^2 > K_{obs}$, then just as in the above case, only the first member will be retained.

$K_1 \to 0$, the functional group in the polymers does not markedly react with the catalyst.

For film of thickness l:

$$C_n = K_{obs}C^0_{cat}t\left\{1 - \frac{8}{\pi^2}\sum_{m=0}^{\infty}[1 - \exp(2m + 1)^2_y]\frac{1}{(2m + 1)^4 y}\right\} \quad (7)$$

where $y = \pi^2 D_{cat}t/l^2$.

For the initial period of degradation:

$$C_n = \frac{4}{\pi^{1/2}} K_{obs}C^0_{cat}D^{1/2}_{cat}l^{-1}t^{3/2} \quad (8)$$

For filament of radius r:

$$C_n = K_{obs}C^0_{cat}\left\{t - \sum_{n=1}^{\infty}\frac{4r^2}{\mu_n^4 D_{cat}}\left[1 - \exp - \left(\frac{D_{cat}}{r^2}\mu_n^2 + t\right)\right]\right\} \quad (9)$$

Here again it will surface to retain only the first member of the series.

4.2 Internal Kinetic Region

At low transformation levels we get the film and filaments:

$$C_n = K_{obs}C^0_{cat}t \quad (10)$$

4.3 External Diffusive-Kinetic Region

The degradation occurs in a certain thin reaction surface layer, of a size mostly undeterminable because of the absence of K_{obs} and D_{cat} values. This layer usually assumed to be infinitely small and degradation will then occur virtually from the surface of the polymer implant.

For film of thickness l:

Thickness variations are obtained by equation:

$$l = l_0 - K^s_{obs}C^s_{cat}\frac{t}{\rho} \quad (11)$$

where K^s_{obs} is the degradation rate constant at the polymer surface; C^0_{cat} the catalyst concentration at the polymer surface; and ρ the polymer density.

The variations in mass are found from the equation:

$$m = m_0 - K^s_{obs}C^s_{cat}St \quad (12)$$

where S is the sample area contacting with the medium.

For filament of radius r:

$$r = r_0 - K^s_{obs} C^s_{cat} \frac{t}{\rho} \tag{13}$$

$$m^{1/2} = m_0^{1/2} - K^s_{obs} C^s_{cat} \left(\frac{\pi l}{\rho}\right)^{1/2} t \tag{14}$$

4.4 Specificities of Degradation of Heterogeneous Polymers

Polymer implants invariably display anisotropic structural characteristics and properties (structural gradients) relative to volume.[21]

In a single-phase system such structural gradients are glass-like and are observed in highly elastic sites, strongly and weakly cross-linked region, oriented and non-oriented region and regions with different molecular mass distribution (MMD).

Heterophase systems contain amorphous and crystalline region and regions with varying stereo- and chemical structures.

In the general case, the polymer regions show different reactivities (different K) and different capacities to sorb and conduct aggressive media (different C^0 and D). Thus, the total destruction rate is:

$$W = \sum_i^{\infty} [K(C_n^0 - C_n)C_{cat}]_i V_i \tag{15}$$

where V_i is the relative size of each region.

The expression (15) shows that degradation may occur at various rates in different sites of the polymer product, i.e. one may observe "polychromic" degradation kinetics in solid polymers.

All functional groups in polymers can conventionally be classified as "accessible" and "inaccessible." Usually functional groups in amorphous regions and over the lamella surface are accessible in amorphous-crystalline polymers. The accessibility is always determined for a specific reactant. For example, functional groups in the same region may react with water molecules and be inert to salt ions.

5. CATALYTIC ACTIVITY OF BIOLOGICAL MEDIA

When polymers are in contact with biological media, the latter medium catalyze reactions involving chemically unstable bonds in the polymers. Biological media contain a large number of low-molecular and high-molecular substances of different chemical nature, and these substances show different catalytic activities for different polymers.

Analysis of various reported results showed that three classes of substances, namely water, salts and enzymes are most suitable for studying the catalytic activity.

5.1 Water

The water content in biological media is high. For example, the human living body contains from 45 to 75% water, which is concentrated in the intracellular fluid, tissue fluids and plasma. Thus in any part of the living body, polymers will contact water. Numerous data on water sorption and diffusion in various polymers have been reported. Table III lists the data for polymers used in medicine and it shows that water activity diffuses through all polymers; however, the amount of sorbed water varies widely. The following characteristic features will be noted:

1. In amorphous-crystalline polymers, sorbed water is localized primarily in the amorphous regions of the polymer.
2. Double sorption occurs in hydrophobic polymers at temperatures below their glass-transition temperature. It represents in fact the occupying of micropores and dissolution in the matrix of the polymer.
3. In hydrophilic polymers, the water diffusion coefficient depends on the water content in the polymer.

Heterochain polymers and some carbochain polymers with heteroatoms in the side radicals are unstable relative to water. Carbochain polymers are stable in water.

In most polymers, the water diffuses at a sufficiently high rate to be sorbed in relatively large amounts. Thus, for filaments and thin films, one can expect that

TABLE III

The water sorption and coefficient diffusion in the polymers used in medical practice

Polymer	$C^0_{H_2O}$, g/100 g	*t°, C	$D \cdot 10^9$, cm²/s	t°, C
Segmented polyurethanes				
Avcothane-51	1.2	37	400	37
Biomer	1.0	37	700	37
Polyacrylonitril*	7.5	25		
Polyvinil alcohol*	4.0	25	0.051	25
Polyvinilchloride*	0.5	30	23	30
Polydimethylsiloxane*	0.07	35	70000	35
Polydodecaneamide*	2	30	3.9	30
Poly(-2-hydroxyethyl-methacrylate), Hydron	40	37	100	37
Polyglycolide	8	37	5.0	37
Polycaproamide**	8	35	1.2	35
Polycarbonate	0.3	37	66	37
Polyglactine	8	37	7.0	37
Polymethylmethacrylate*	1.2	50	130	50
Polypropylene*	0.07	25	240	25
Polytetraphtroethylene*	0.01	20		
Polyethylene (δ = 0.923)	0.006	25	230	25
Polyethylene therephtalate	0.3	25	39	25

*From Reference 22.
**From Reference 23: the others—private data of authors.

TABLE IV

The values of $K_{obs}\ C^0_{H_2O}$ at 37°C and of the energy activation of the different heterochain polymers

Polymer	$K_{obs}C^0_{H_2O}$, min^{-1}	E_{H_2O}, cal/mol	Reference
Polydodecaneamide	$4 \cdot 10^{-11}$	—	*
Polyglycolide	$9 \cdot 10^{-4}$	—	*
Polycaproamide	10^{-10}	—	26, 27
Polycarbonate	$3.3 \cdot 10^{-6}$ at 70°C	23 ± 1	28
Polyglactine	$1.5 \cdot 10^{-3}$	—	*
Polyethylene therephtalate	10^{-10}	25 ± 2	*

*Private experimental data of the authors.

degradation will occur in the internal kinetic regions and the concentration of degraded bonds in the polymer can be found using Equation (10).

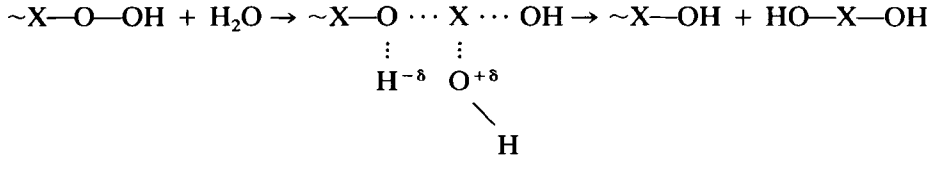
Table IV lists the values $K_{obs}C^0_{H_2O}$ at 37°C and activation energies for degradation of different heterochain polymers.

For partially cross-linked polydimethylsiloxane the amount of sorbed water is negligible and the degradation process will occur mostly in the external diffusive-kinetic region, the changes in the polymer mass being described by Equation (12). The values of K_{obs} at 37°C and of the activation energy are $2 \cdot 10^{-5}$ g/cm^2 · day and 14 kcal/mol, respectively.[29]

Thus, for some polymers, e.g. polydlycolide, polyglactine the degradation in water occurs at a high rate, and this must be taken into account when examining the general diffusion kinetics of these polymers in biological media, and selecting the sterilisation technique (these polymers cannot be sterilised with water vapor).

Hydrolytic destruction of carbonyl-containing polymers (polyamides, polyesters, polycarbonates) occurs by the mechanism of bifunctional catalysis.

Hydrolytic degradation of oxygen-containing polymers (polydimethylsiloxane) occurs only from the end of the chain (depolymerisation) and apparently by mechanism.[30]



5.2 Salts

Biological media contain large amounts of salts. Table V shows the ionic content of the human body liquid.[31] Plasma and intracell liquid also have proteins in an anion form (they contain carboxylate groups). The next section is devoted to proteins, and these will not be discussed here.

Salt diffusion and sorption in various polymers have been described in detail,[20,32] and only their characteristic features will be discussed here. When electrolytes diffuse in hydrogels (poly-2-hydroxyethylmethacrylate, polyvinyl alcohol, etc.), their thermodynamic parameters (for example, D) are close to those in solutions. In hydrophilic polymers to some extent dissolving water, the sorbed water does not

TABLE V

Ionic composition of the human body liquid, mekv/l

Ion	Plasma	Tissue liquid	Intercellular liquid
Na^+	138	141	10
K^+	4	4.1	150
Ca^{2+}	4	4.1	40
Mg^{2+}	3	3	40
Cl^-	102	115	15
HCO^-	26	29	10
PO_4	2	2	100
SO_4^{2-}	3	1.1	20
Organic acids	3	3.4	—

occupy a continuous space in the polymer matrix, and ions diffuse by activated jumps between polar groups to result in reduced electrolyte C^0 and D compared with the same parameters in the solution. Diffusion of electrolytes in hydrophobic polymers occurs by a mechanism similar to transfer of gases and vapor. Hence, for electrolytes with high vapor pressure (e.g. for hydrochloric acid) C^0 and D are close to those for water in these polymers. Electrolytes with low vapor pressure (e.g. salts of hydrochloric and phosphoric acids) are characterised by extremely low C^0 and D values, i.e. they virtually do not sorb in hydrophobic polymers.

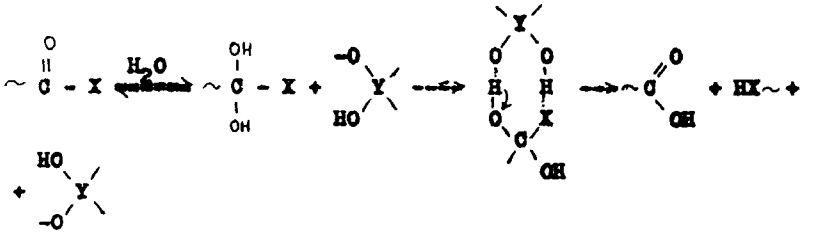
Thus, one may conventionally separate all polymers into two groups: those that dissolve and those that do not dissolve salts. The first group involves polymers with $C^0_{H_2O} > 1$, and the second those with $C^0_{H_2O} < 1$.

The study of the catalytic action of salts on polymers is only beginning. We have investigated the effect of the salts in Table V on several polymers.

The degradation of moderately hydrophilic polymers (polyglycolide and polycaproamide) becomes considerably faster with an increased concentration of acid phosphates, bicarbonates and bisulphates in buffer solutions at constant pH (Figure 2) and (Figure 3).

However, salts of monobasic acids virtually do not catalyze these polymers.[33]

Hence, the following gradation can be made relative to ions: the anions of monobasic acids and the cations listed in Table V are catalytically inactive. The general schema of carbonyl-containing polymer catalysis is:



This bifunctional catalysis is very unlikely with non-carbonyl-polymers, e.g. polydimethylsiloxane, as confirmed experimentally.[29]

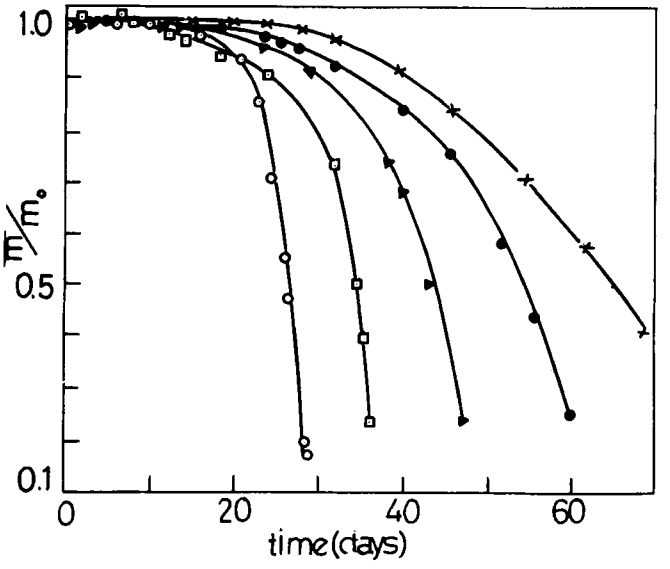


FIGURE 2 The mass of the polyglycolide suture against implantation period and incubation time in model media at pH 7.4, 37°C: ○—1 mol phosphate buffer; □—living body (rabbit); △—0.5 mol phosphate buffer; ●—0.1 mol phosphate buffer; × —water.

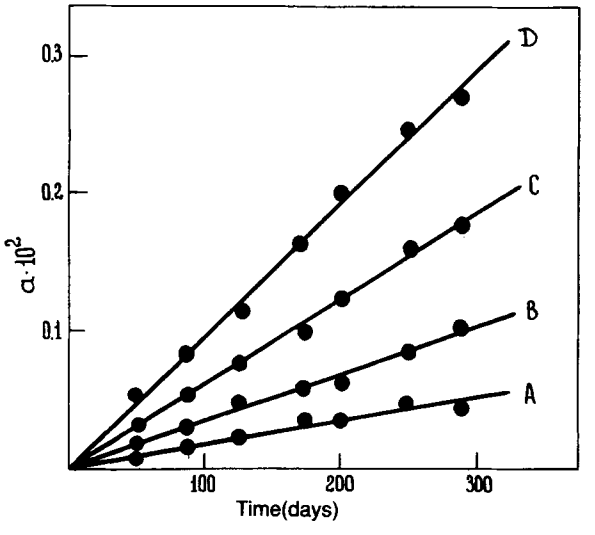


FIGURE 3 The time dependence of the conversion degree of PCA amide bonds at 100°C by action of different concentration of phosphate buffer at pH 7.4 (A—0.1 mol; B—0.3 mol; C—0.6 mol; and D—1 mol).

Thus, for some carbonyl-containing polymers, salts, chiefly phosphates, exert a substantial catalytic effect at physiological concentrations.

5.3 Enzymes

The role of enzymes in the degradation of polymers implanted in the living body, (unlike that of water and salts), has never been in doubt. Yet, a firm experimental evidence of their effect has not been obtained so far. The typical results for medical polymers are shown in Table VI.

TABLE VI

The change of the relative IRS absorption of the polyurethane adhesives KL-3 in the model system and subcutaneous fat of the rat, p. 63[35]

Medium	$W \cdot 10^2$, day^{-1} 1110 sm^{-1}	1230 sm^{-1}	1730 sm^{-1}
Saline solution	0.13	0.05	0.04
Ringer-Lock solution	0.13	0.04	0.03
Extract from rabbit liver	0.10	0.04	0.02
Extract from rabbit kidney	0.12	0.02	0.02
0.01% solution of trypsin	0.11	0.01	0.02
0.01% solution of chemotrypsin	0.12	0.01	0.02
Living body	0.59	0.39	0.34

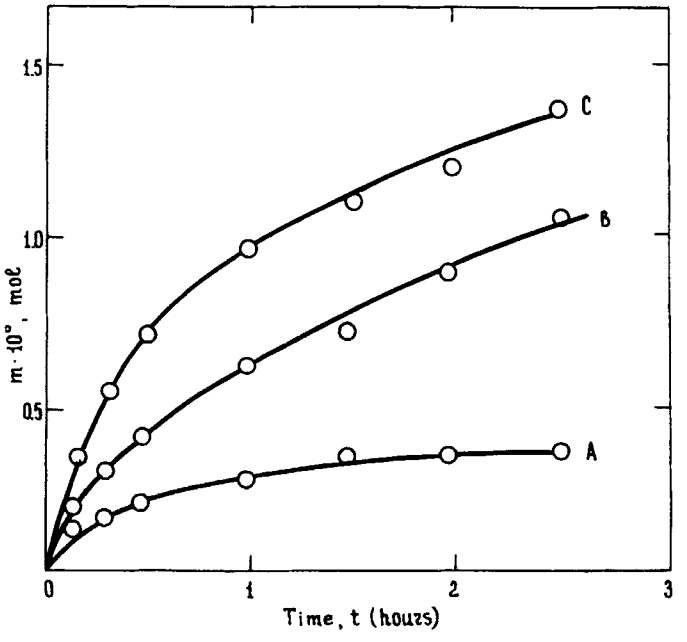


FIGURE 4 Discharge of glycolic acid from polyglycolide vs time incubation in the water solution β-glucoururinidase at 37°C: A—enzyme concentration 1 mg/ml without inhibitor; B—in the presence of inhibitor 0.5 mg/ml; and C—inhibitor concentration 1.8 mg/ml.

The data showing that respective media do not simulate the high degradation rate in the living body can be interpreted as follows.

Enzymes catalyzing degradation dissolve in the capsule and represent chiefly lysosomal enzymes discharged by macrophages and other cells.

Salthouse[3] used methods of quantitative hystoenzymology to determine the activity of various enzymes in the capsule on the surface of polymers after implantation in rats at different times. All materials showed increased enzyme activity in thirteen days, this being due to higher phagocytosis in the implantation zone. After the operation wound heals to form a connective tissue capsule, a stationary enzyme concentration seems to set in the polymer surface.

Enzymes readily diffuse in the capsule and can be adsorbed in varying concentrations. For instance, the surface concentration of catalytically active enzymes depends not only on their amount in the capsule volume, but also on the competing adsorption of other proteins (catalytically inactive plasma proteins, lipids, etc.).

The enzyme action mechanism of polymers is unusually complex and still obscure, since most synthetic polymers do not represent specific substrates for enzymes.

Experiments confirming the effect of enzymes on polyglycolide are known at present. Figure 4 shows kinetic curves for discharge of glycolic acid in the degradation of polyglycolide filaments in solutions with a varying β-glucouronidase activity.[37] The initial degradation rate increases in proportion to the enzyme activity; if an inhibitor (iodacetamide) is added to these solutions, the catalytic activity of β-glucouronidase falls practically to zero. Williams[38-40] found for the breaking of polyglycolide filaments in various enzyme solutions, that carboxypeptidase A, trypsin and leucine aminopeptidase have a marked accelerating effect on the degradation of this polymer.

Catalytically active enzymes have not been specifically identified for other polymers, though many hypotheses on this subject have been put forward.

Thus, enzymes, along with water and phosphates, are the principal agents that catalyze polymer degradation in biological media.

6. THE FATE OF DEGRADATION PRODUCTS IN LIVING BODY

As a result of degradation, polymer breakdown products are removed from the living body by a two-phase process of metabolic change and conjugation; this results in formation of metabolites and conjugates, in urine, bile or exhaled air, p. 8.[41]

Metabolic changes are responses inducing one or several conversions of the reaction products (oxidative, hydrolytic, etc.) that lead to the appearance of functional groups enhancing molecule polarity.

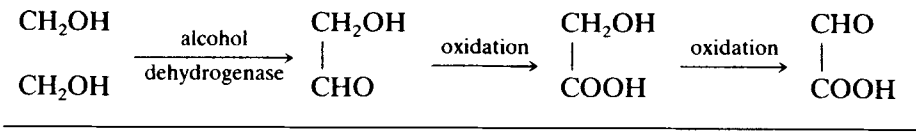
Conjugation represents the addition of degradation products or their metabolites to biologically active substances in the living body, thus making the molecules more polar and less fat-soluble and, hence, readily dischargeable. Table VII lists some heterochain polymers used in medicine and their decomposition products.

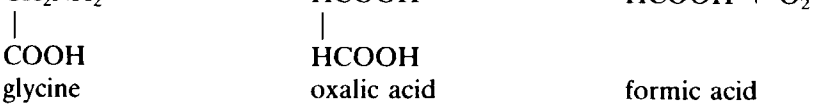
All degradation products may be classified as three groups: (a) those that take direct part in metabolic processes; these are basically nontoxic; (b) those that are subjected to metabolic or conjugative transformations; for example, ethylene glycol transforms in the living body as p. 259[41]:

TABLE VII

Composition products, K_{dis} and dissolution in the water of the heterochain polymers

Polymer	Destruction products	K_{dis}	Dissolution in water
Polyglycolide	Glycolic acid	$1.5 \cdot 10^{-4}$	good
Polyglactine	Glycolic and lactic acids	$1.4 \cdot 10^{-4}$	good
Polydodecaneamide	Aminocapronic acid	$1.4 \cdot 10^{-5}$	bad
Polycaproamide	Aminoundecane acid	$1.4 \cdot 10^{-5}$	good
Polydimethylsiloxane	Mixture siolen and its cycles	—	—
Polyethylene therephtalate	Therephtalic acid, ethyleneglycol	$2.9 \cdot 10^{-4}$ $3.5 \cdot 10^{-5}$	bad good





The toxic effect of the ethylene glycol is due to kidney damage caused by oxalate deposits in small renal channels: (c) those discharged from the living body mostly in an unchanged form; for example, terephthalic acid $K_{dis} = 3.10^{-4}$) is a sufficiently polar substance that cannot readily penetrate the tissues and be rapidly discharged through the kidneys, this acid might form a complex with albumin (with an amino group of asparagic acid) circulating along the vascular system, the compounds that are metabolically inert and at the same time non-polar, vinyl chloride for instance, are discharged with difficulty and accumulate in fatty tissues.

7. BIOCOMPATIBILITY AND BIODEGRADATION OF VARIOUS CLASSES OF POLYMERS

Publications devoted to quantitative biocompatibility and biodegradation of the principal classes of medical polymers are becoming available. Various approaches to the study of these polymers and the principal results obtained by various authors are discussed below.

7.1 Polyamides

7.1.1 Polycaproamide. Polycaproamide (PCA) was one of the first polymers used for medical purposes due to its chemical structure, which is close to the elemental link in the polypeptide chain PCA is used to a limited extent in the form of surgical suture (produced by Ethicon and the Soviet medical industry).

PCA may be considered a biocompatible polymer: hystological data are indicative of insignificant inflammation around the implant.[33,42,43]

In regard to resorption time (life time) in the living body, PCA belongs to polymers with an average resorption time. Consequently it can be used as a model for in vivo investigations. Detailed data therefore, exist for the macrokinetics of PCA degradation in the living body, but also for media.[33,34,36,44]

As follows from the above papers, the degradation occurs by a joint mechanism: both from the surface and in the polymer bulk. These studies were the first to analyse the catalytic effect of water and salts (phosphates and carbonates) in the course of degradation. PCA degradation in the living body results in changes of the mass and molecular mass due to degradation of accessible amide bonds in polymer amorphous regions (Figure 5).

It was noted that a distinct feature in PCA degradation is that the total polymer surface remains practically unaltered in the course of degradation since the decrease in the filament diameter is compensated by the increase of the surface through formation of cracks and irregularities.

Changes in the polymer mass are described by the equation:

$$m = m_0 - K^s_{obs} \cdot t \tag{16}$$

where $K^s_{obs} = K^s \cdot C^s_{cat} \cdot S$, m_0 and m are the initial and current mass of implant, K^s = the rate constant of surface implant degradation, C^s_{cat} = the catalyst constant on the surface S. The value estimated from experiments using rabbits is (1.6 ± 0.2) g·day^{-1}, and the value of $K_{obs(rand)}$, the degradation rate constant of amide bonds in the polymer matrix, estimated from the titration data for the end amide groups of the implanted samples is:

$$K_{obs(rand)} = (5.4 \pm 0.5) \cdot 10^{-5} \text{ day}^{-1}.$$

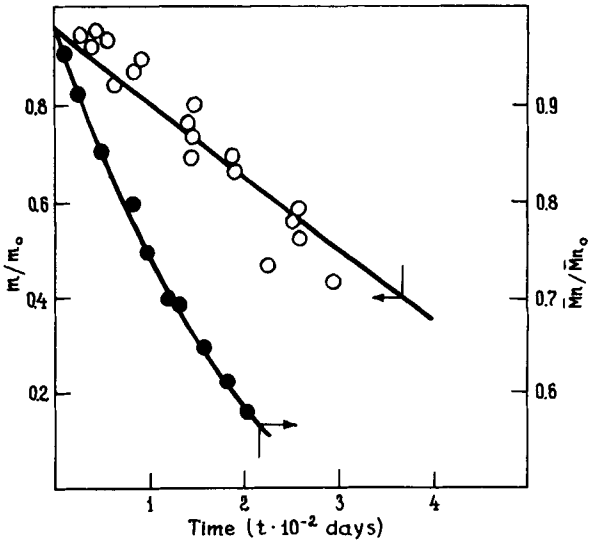


FIGURE 5 The change in mass and molecular weight PCA nets subcutaneously inserted in the back of rabbits vs time.

An analysis of the action of catalysing agents showed that PCA degradation in the bulk is caused by water, the solubility of which in PCA is (5.5 ± 0.5)%.

The high water content in the polymer favors salt penetration into PCA with a diffusion coefficient 10^{-9} sm^2/sec.[45] The constant of the amide bond degradation rate in the amorphous region under the effect of water at 37°C is 1.10^{-7} day^{-1}; with this value of the rate constant, only $0.5 \cdot 10^{-4}$ of amide bonds degrade annually, this being much less than the rate constant observed in the living body.[26] A substantial factor is the contribution of salts to the polymer degradation in the bulk. From model experiments in 0.1 M NaH_2PO_4 (concentration in intra cell liquid) at 37°C, $K_{obs(rand)}$ was found to be $(0.5 \pm 0.1) \cdot 10^{-5}$ day^{-1}.

A special experiment showed that enzymes for 100 days do not penetrate the PCA films of a thickness equal to the filament diameter. It seems that enzymes can take part in degradation only at the surface. Thus, V-type degradation is caused by water and salts in the living body, and S-type degradation by enzymes.

The above quantitative data permit prediction of the PCA lifetime (tensile strength) in the living body. From the obtained macrokinetic parameters it becomes clear that the use of PCA as a new type of surface should be limited because of its short lifetime. PCA will therefore, be replaced with more reliable sutures such as Dexon and polyglactine that appeared on the market in the last decade.

7.1.2 Polydodecane amide. Polydodecane amide (polyamide 12) is used for endoprostheses to a lesser extent. Its lifetime in the living body is longer and it is therefore considered to be basic for various structural modifications in obtaining novel materials for endoprosthetics.[46-49]

The nature of degradation appeared to be similar to that of polycaproamide. When implanted, the polymer loses in part its molecular weight mass, tensile strength and diameter of the filament becomes smaller; this is accompanied by appearance of cracks on its surface. As was to be expected, the degradation mechanism is similar to that for PCA in the living body, i.e. it occurs over the amorphous regions of polyamide-12 (IR spectroscopy and X-ray diffraction analysis data)[48] under the action of the same catalysing agents salt and enzymes just as for PCA.

7.2 Polyesters

7.2.1 Polyglycolide. Polyglycolide (PGL), a glycolic acid polycondensation product, the first synthetic polymer that was synthesised for medical purposes at the end of nineteen-sixties by American Cyanamid, Co. The synthesis principles and structural features of polyglycolide were outlined in numerous studies.[50-54] PGL is used in diverse fields of medicine: orthopaedics and traumatology (in manufacturing pins, plates, studs, needles, bone substitutes), and ophthalmology (for surgical suture, sponges, and powders for wounds and burns). Its great merit is also that it can be used in biocomponent systems as the resolving part of the prosthesis.

Such a wide use of PGL is due to its good compatibility in the initial moment of implantation, irrespective of its form (block, powder, fiber), and also to the fact that the sole degradation product—glycolic acid—is readily metabolised, degrading to water and CO_2.

Hystological studies of PGL at the initial, intermediate and end stages showed the absence of any trend towards cell increase, which is characteristic of specific inflammation response. A well-formed connective-tissue capsule appears around the implant.[55-57]

Ever since PGL was synthesised, numerous investigations concerned with its degradation have been published. The behaviour of PGL surgical suture called Dexon (Check and Davis Cyanamid) has been studied most exhaustively.[5,40,58-60]

Papers dealing with the kinetics of PGL degradation in the living body and model media have appeared in the recent years.[37,40,61-64] These discussed the macrokinetics of degradation in the living body and in vitro, and elucidated the catalysing compounds in the living body and the contribution of each component to the process of degradation.

The following summarizes the principal results[62]:

1. In the living body sutures degrade in an unusual manner: microphotographs reveal transverse splitting into fragments of 1 mm at a constant diameter of the filaments by the 15th–18th day of implantation.

2. By that time, the filament tensile strength is found to be completely lost.

3. The macrokinetic curve for mass loss in the living body (Figure 2) is complex. It is specified by an insignificant change in the initial implantation stages, and a sharply increasing mass loss in 20 days.

4. The shapes of kinetic curves of mass losses in water, phosphate buffer and carbonate buffer at pH = 7.4 and 37°C coincide with those of the kinetic curve for the living body.

5. In vitro experiments of incubating PGL sutures in proteolytic enzyme solutions showed β-glucuronidase to be active (Figure 4).

A degradation mechanism based on the experiments is suggested. It involves two-stage degradation of a highly crystalline polyester (degree of crystallinity ~0.8).

At the initial implantation period the water is absorbed in the amorphous regions, and the polymer slowly degrades, chiefly under the action of water. As seen from the curve for mass loss in the living body the degradation rate sharply increases after reaching a 0.2 extent of conversion. This is due to degradation of the crystallite even on the surface under the action of sorbed water, salts, and enzymes. The observed rate constants of ester bond breaking under the action of water, salts and enzymes can be obtained from in vitro experiments (Table VIII).

TABLE VIII

The values of the rate constants of the ester bonds of the polyglycolide under action basic components organisms environment defined from in vitro experiments at 37°C

The rate constant	Value
$K^{v}_{H_2O}$	$5.0 \cdot 10^{-2}$
$K^{s-v}_{H_2O_4^-}$	$4.2 \cdot 10^{-2}$
$K^{v}_{H_2PO_4^-}$	$5.0 \cdot 10^{-2}$
$K^{s-v}_{H_2PO_4^-}$	$4.2 \cdot 10^{-2}$
K^{s-v}_{enz}	$1.0 \cdot 10^{-2}$

The general equation derived from the above-cited results is:

$$m/m_0 = 0.2-0.2(1 - \exp(K^v_{H_2O}C^v_{H_2O}t)) + 0.8\left(1 - \frac{K^{s-v}_{H_2O}\cdot C^{s-v}_{H_2O}\cdot t}{Nb_0\rho}\right)^2$$
$$+ 0.2(1 - \exp(-K^v_{H_2PO_4-}\cdot C_{H_2PO_4-}\cdot t)$$
$$+ 0.8\left(1 - \frac{K^{s-v}_{H_2PO_4-}\cdot C^{s-v}_{H_2PO_4-}\cdot t}{Nb_0\rho}\right)^2 + 0.8\left(1 - \frac{K^{s-v}_{cnz}\cdot C^{s-v}_{cnz}\cdot t}{Nb_0\rho}\right)^2 \quad (17)$$

where m_0, m are the initial and current polymer mass; N the number of crystallites in the cross section, ρ = the polymer density; b_0 the transverse crystallite size; K^v the observed rate constant of PGL ester bonds breaking in the polymer amorphous regions under the action of water and salts; K^{s-v} the observed rate constant of degradation on the crystallite surface: 0.2 the volume of the amorphous regions, and 0.8 the volume of the crystallite regions; C^v the average catalyst concentration of water, salts, enzymes in the polymer matrix; C^{s-v} denotes the catalyst concentration in the lateral face of the crystallites. A numerical solution of the inverse problem using the above rate constants, and random selection of the enzyme concentration values in rabbit body (no accurate data have been reported) permitted reproducing the living body experimental curve.

A quantitative analysis of the macrokinetics of PGL suture degradation permits us to predict the kinetic degradation curves and the polymer lifetime relative to mass of various diameters in different parts of the living body (with varying enzyme and salts contents).

7.2.2 Polyglactine. Polyglactine (PGLC) is a dissolving surgical suture representing a copolymer of glycolic and lactic acids (Ethicon). The degradation products of this polymer in living body are the glycolic and lactic acids, involved in metabolism, as the case of PGL. Hence items from PGLC (surgical sutures and pellets) display good compatibility with the organism tissues when subjected to hysto-morphological tests.[3,66-70]

In principle, there should be no difference between PGL and its copolymers both in the degradation mechanism and destruction rate. In subcutaneous fat of rats, the degradation of the lactic acid homopolymer is slower than that of PGL, apparently because of the lower water solubility in polyglactine.[71] PGLC samples with different PGL to polylactide ratios have different half-lives that were estimated from the presence of labelled ^{14}C in various rat organs, from several months to one week for the homopolymer.

To elucidate the role of cell enzymes in PGLC 910 resorption Salthouse *et al.*[72] investigated in detail the subcutaneously implanted PGLC 910 (Ethicon) degradation in rat. It was concluded that the enzymes were not involved in the initial degradation stages.

The somewhat increased activity of dehydrogenase and cytochromoxydase in 40 days of implantation leads to metabolites according to the following scheme[72]:

$$\text{PGLC 910} + \text{water} \rightarrow \text{lactic and glycolic acids} \rightarrow \xrightarrow{\text{oxyreductase}} CO_2 + \text{water}$$

It will be noted that PGLC is the only polymer for which not only the degradation kinetics, but also the dynamics of the metabolism of the degradation products have been studied.

The mass loss curves for the living body, water, and different buffer solutions of varying concentrations (Figure 6) are similar to the kinetic curves for PGL.[62] One can note a slight acceleration in the degradation process compared to that of PGL; this was also noted elsewhere.[71] Possibly, this is due to the somewhat disordered crystalline regions in the polymer caused by changes in the parameters of the copolymer crystalline unit.

The equation that quantitatively describes the PGLC destruction process is similar to Equation (17).

Synthesis of these types of copolymer is more promising, than that of PGL, because they open up wider opportunities for obtaining surgical materials with a broad lifetime spectrum.

7.2.3 Polyethylene terephthalate. Items from polyethylene terephthalate (PET) in the form of nets, sutures and vascular prostheses occupy a firm place in surgical practice, because they retain their properties for a long period of implantation, and because of their good biocompatibility.[73–76]

A large number of papers[77–79] is devoted to hystological compatibility; it has been established that in all cases the PET implants cause minimum tissue response, which is characterised by a thin capsule and normal connective tissue around the prosthesis for a long period of time of up to 5 years.

However, the presence of macrophages was noted after some years implantation, this being apparently caused by the effect of terephthalic acid on the surrounding tissues.[80]

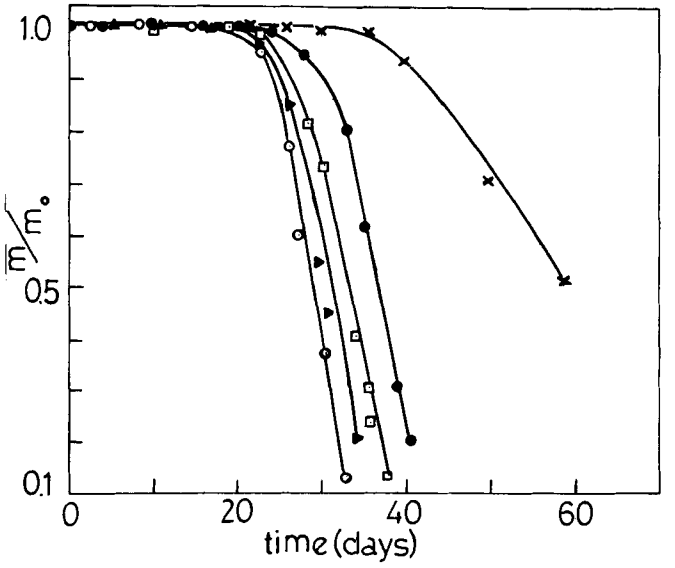


FIGURE 6 The relative mass against implantation time of the polylactide suture in the rabbit and incubation time in the buffer system at 37°C and pH 7.4: ○—1 mol carbonate buffer; ▼—living body; □—1 mol phosphate buffer; ●—0.5 mol phosphate buffer; and × —water.

Macroscopic observations[75] of changes in the properties of vascular prostheses implanted in the human body for various implantation times have also been discussed and virtually no marked changes were observed for up to five years. After being in the human body for 8 and 11 years, the prosthesis surface was found to develop cracks and simultaneous thinning of the filament.

Systematic studies of degradation processes in PET nets implanted subcutaneously in rabbits, dogs and humans (substitution of abdominal defects) were conducted[81-83] to determine the lifetime of the PET prostheses.

As described above, at 37°C PET is a polymer resistant to water; however, it degrades by the S-type in base media (when the reaction rate is higher than the aggressive medium diffusion rate) and by the V-type in acid media (when the reaction rate is lower than aggressive medium diffusion rate).

Analysis of the data on degradation of PET prostheses used for substitution of the abdominal wall defects showed that both types of degradation can occur depending on the living body condition.

When the pH of the prosthetic-surrounding medium is 7.0–7.4, the changes in the macrokinetic parameters (mass and radius) are described by Equations (11) and (12), and the tensile strength by:

$$P = P_0(1 - K^s_{obs}t/r_0)^2 \tag{18}$$

where P_0 and P are the initial and end values of tensile strength. The linear

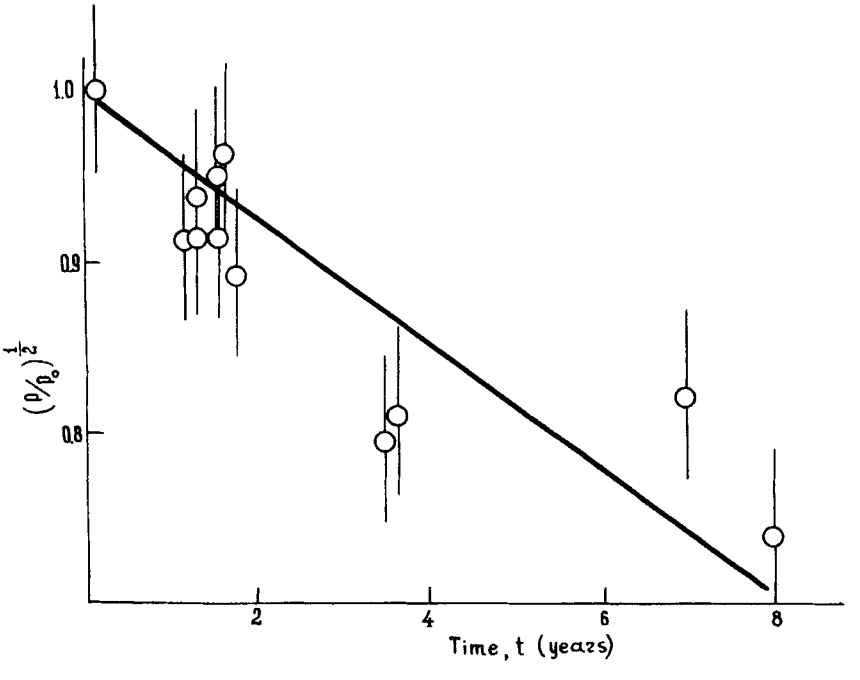


FIGURE 7 The relative tensile strength of the PET filaments vs implantation time under normal conditions (without infection).

dependence of $P^{1/2}$ on t permits predicting the lifetimes under these conditions; these are 30 ± 5 years (Figure 7).

A V-type PET degradation was found for the first time in analysing the properties of prostheses in the course of acute inflammation characterized by acid pH (4.8–6.8), and probability induced by bacteria found in and around the prosthesis.[80] Under these conditions the prosthesis samples showed complete loss of tensile strength after 1–2 months of implantation in the living body; this was accompanied by a sharp change in the molecular mass due to breaking of ester bonds in amorphous regions, as described by equation[84]:

$$M_{n_0}/M_{n_t} - 1 = k^{v}_{obs} M_n t \tag{19}$$

where M_{n_0} and M_{n_t} are the values of the initial and current number average molecular mass; K^{v}_{obs} the bond breaking rate constant of in the polymer amorphous regions (Figure 8).

These data show that the degradation mechanism affects primarily the medium pH, and that the equations for prediction of lifetime, (11), (12) and (18), refer to a case where the implant surrounding is normal (pH 7.0–7.4).

As for the involvement of catalytic agents in the biological body medium, it appears that in the case of PET, water has no catalytic effect ($K^{37°}_{obs}$ 10^{-9} + 10^{-10} min^{-1}, and 10^{-3} esters bonds break in 10 years) p. 177.[20] Phosphate ions practically do not penetrate into the polymer matrix; hence, under their action degradation will occur on the surface. Enzymes of the body medium seem to participate in degradation on the surface, just as for PGL and PCA.

Hence, when the prosthesis surrounding is "normal" (pH 7.0–7.4), degradation of PET prosthesis will occur under the action of salts and enzymes. But, if the prosthesis has a "pathological" surrounding (acid medium), acids can appear to be catalytically active; in this case, acids are the only really active substances causing polymer degradation in bulk due to the ability of acid protons to diffuse in the polymer matrix,[85] the K^{v}_{obs} = (1.1 ± 0.5) $years^{-1}$.

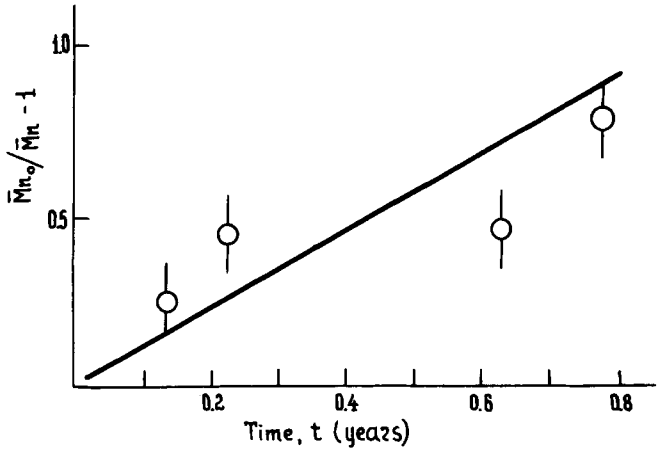


FIGURE 8 The degree of conversion on molecular mass of PET prostheses in the presence of bacteria.

This helps understanding the results in paper[40] on PGL degradation in bacterial culture media, namely that PGL does not degrade in the presence of bacteria. Indeed, in an acid medium PGL degrades at a hydrolysis rate close to that in water while the opposite is observed for PET. According to papers,[83,86] the enzymes produced by bacteria and various low-molecular substances (preferentially acids that change the medium pH), are the basic active degrading agents of the bacterial medium.

7.3 Polyolefins

7.3.1 Polypropylene. Polypropylene (PP) was first used for medical purposes because of its high chemical resistance and good mechanical properties. In the early seventies, it was used for lining artificial heart valves and for ball joint prostheses. At present, PP sutures are manufactured by Ethicon.

Hystological evidence shows that, unlike PP-containing catalysts and stabilizers,[88] "medically pure" PP causes moderate response in the tissues of a living body.[3,5,87]

By virtue of its chemical structure, PP can be subjected to only oxidative degradation. Hence, PP can be expected to last in tissue of a living body and to degrade slowly only under the effect of oxidative enzymes in the presence of oxygen dissolved in the body tissues.

The general picture of PP suture and film degradation in the living body is characterized by the following features:

1. Impairing of the mechanical properties (reduced tensile strength and relative elongation).[78]
2. Crack formation in the initial implantation stages and fragmentation of the polymer implant in more remote stages[58]; PP samples without antioxidants display earlier fragmentation.[78]
3. The PP molecular mass remains practically the same during all implantation periods.
4. After implantation, the PP sample IR spectra showed an absorption band associated with the carbonyl groups.[89]
5. The implant-surrounding capsule was noted to have an increased activity of oxyreductase and cytochromoxydase.[3]

It follows from the above experimental observations on PP degradation in the living body that PP degrades by the S-type under the action of oxidative enzymes which do not penetrate into the polymer matrix. Oxidative degradation is known[90,91] to be accompanied by breaking of the main polymer chain and should cause a decrease in the molecular mass. However, since catalyzing agents do not penetrate into the polymer bulk, surface bond breaking does not contribute significantly to the reduction of the molecular mass. Oxidation-induced accumulation of carbonyl compounds also seems to occur at the crack surfaces, not over the entire bulk (matrix).

Specific experiments using PP incubated in a cytochrome-oxydase solution did not bring the anticipated result because of the rapid enzyme inactivation in in vitro tests. Hence, it would appear advisable to run experiments with bacteria that generate oxidative enzymes breaking the C—C bonds.

7.3.2 Polyethylene. Polyethylene (PE) items have been used in surgery for

twenty years; for example, high-pressure PE (HPPE) (ultrahigh molecular weight PE (UHMWPE) was used in manufacturing hip-joint prostheses. Being a strong non-decomposing polymer, PE is used in ancillary medical equipment (packings and conduction tubes).

Numerous publications, mostly in the fifties and sixties, were devoted to hystomorphological studies of PE. Some authors[93,94] noted that the overall response of the body to PE was not harmful.

For the inverse problem of utilising polymer waste with the aid of microorganisms and bacteria, PE was found to be disappointing. Commercial polyolefins, especially PEHP, appeared to be virtually stable to biosplitting; yet, low molecular fractions are subject to biodegradation by a radical mechanism.[95,96]

It was established that:

1. The basic condition for biodegradation is a large specific area of the polymer, found in powders.[97]

2. The degradation process involves a mass decrease which is accelerated during the initial incubation periods.

3. Carbonyl groups appear in low pressure polyethylene (PELP) samples incubated with microorganisms,[98,99] especially when the introduced fillers are sensitive to oxydases and esterases.

To evaluate quantitatively the biodegradation rate of slowly degrading PE, a sensitive method of analysis using ^{14}C labels introduced by specific synthesis into the PE chain was applied.[99] Samples incubated with microorganisms for various time periods up to three years were subjected to ultra-violet radiation to accelerate the degradation and the loss of mass on account of bacteria and microorganisms was then determined. The value of mass loss due to biodegradation was estimated by extrapolation to zero time radiation. The value of mass loss in three years was 0.5% and was described by Equation (12).

The analysis of these data shows that, like PP, PE degrades by the S-type; the degrading agents may be oxidative enzymes, for which PE is a nutrient carbon medium.

The data on PP and PE degradation, show that although these polymers degrade slowly, their chemical reconstruction during oxidation can lead to unfavorable consequences for the living body.

7.4 Elastomers

7.4.1 Polydimethylsiloxane. Items from polydimethylsiloxane (PDMS) are examples of successful use of synthetic polymers in medicine. The material possesses inertness and satisfactory mechanical properties. It can also be easily processed into desired shapes for various medical items. These include prostheses of different bone and soft tissue elements (in surgery), and ancillary components, e.g. tubes, catheters, shunts and drug carriers. In the sixties, the polymer was commercially developed by Dow Corning with a view to manufacturing a variety of items called Silastic.

During the twenty years of PDMS use, its good compatability was noted in many papers[100,104]; hystological and hystochemical tests of silicone polymers are often employed in checking the compatability of new polymers.

Despite the numerous studies and the extensive experience in utilising silicone polymers, virtually no evidence was reported relative to their degradation in the living body. Systematic investigations on the degradation of vulcanisates of low-molecular PDMS (LMPDMS) were conducted over the past decade [at the Vischnevsky Institute of Surgery].[103,105,106]

In principle, fragments containing bonds may degrade in water.[107,108] The data on LMPDMS degradation at high temperature in water vapor could be quantitatively analyzed under the assumption that two processes, the random degradation and the forming of silanol bonds occur simultaneously[109]:

$$dn/dt = K_{\text{rand}}(C_{n_0} - C_n) \tag{21}$$

where C_{n_0} is the initial concentration of silanol bonds and C_n the concentration of broken bonds by the time t. The depolymerization reaction with silanol bonds as active centers results in loss of polymer mass

$$dm/dt = K_{\text{depol}}C_n \tag{22}$$

where K_{depol} = the rate constant of depolymerization. If the two processes would occur at close rates, the total change in mass may be estimated by (21) and (22), assuming that by random degradation attains low levels; and the reaction occurs in the internal kinetic region:

$$m = K_{\text{depol}}K_{\text{rand}}t^2 \tag{23}$$

Figure 9 shows data on PDMS degradation.

PDMS degradation at temperatures below 100°C was studied in Reference 29. At these temperatures, it is expected that parallel with degradation in the internal kinetic region, the water concentration will be extremely low and the active degradation will take place on the surface.

These types of degradation are classified as follows: if the polymer tensile strength changes, the process occurs preferentially in the bulk and, at σ = const., the process proceeds on polymer surface.

At high temperatures, when water is in the vapor phase, the reaction appeared to occur by the V-type (Figure 10a), and at low temperatures by the S-type (Figure 10b).

In experiments on PDMS degradation, no catalytic effect of phosphate ions was observed in the phosphate buffer; this excludes the possibility of bifunctional catalysis under the effect of the ions contained in the living body.

Hence, the contribution of water to PDMS degradation in the living body should activate the depolymerization reaction of the end groups on the PDMS surface. However, it follows from Figure 9 that there is an essential difference between the degradation rate in the living body and that in water. This difference between the degradation values can be attributed to effect of the enzyme component to the surface depolymerisation reaction. Unfortunately, the enzymes that break siloxane bonds have not been identified so far, and, therefore, a quantitative analysis of

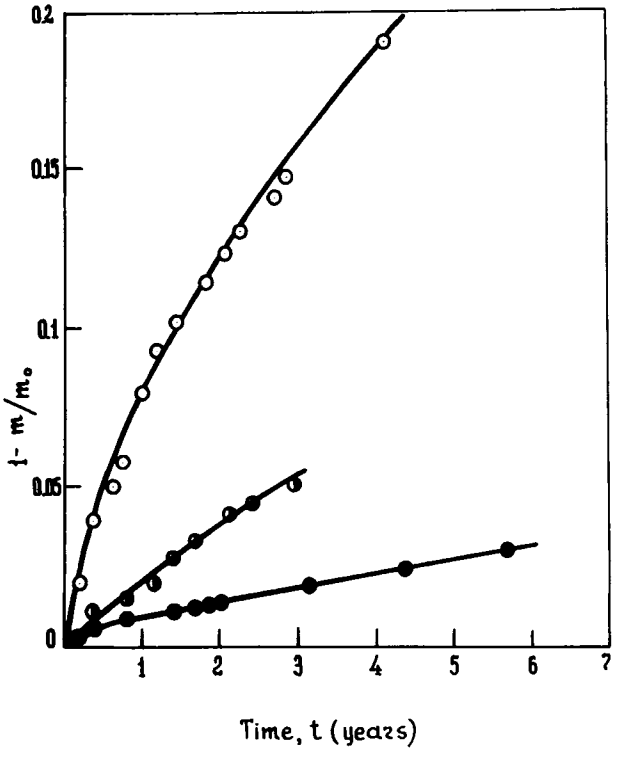


FIGURE 9 The degree of conversion on mass of polydimethyl-siloxane plates vs time at 37°C: ●—air; ◐—water; ○—living body (rabbit).

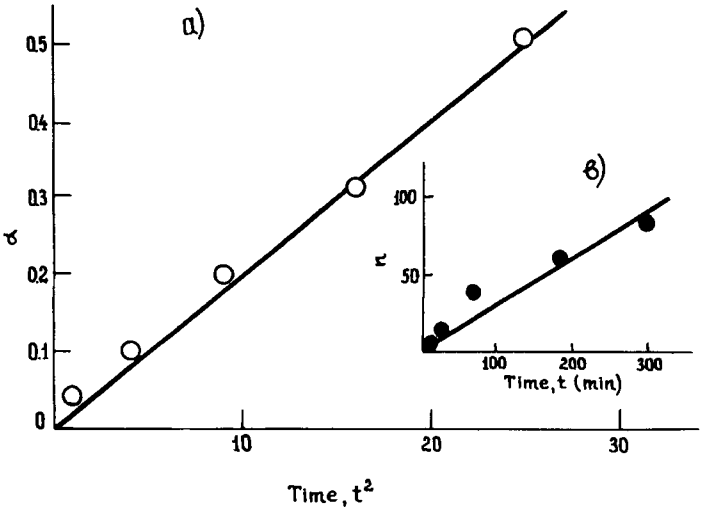


FIGURE 10 a) The degree of conversion on mass of hydrolysed PDMS at 300°C, and b) dependence of the silanol bonds broken by hydrolyse of PDMS at 300°C.

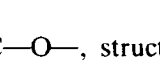
the enzyme contribution cannot be made. The Equation (12) can be used for description the total PDMS degradation in the living body.

The PDMS plate thinning due to mass loss during the degradation in the living body amounts to 20–40 μ/year. It is, therefore, clear that it is undesirable to design PDMS items for long-term use.

Items from organosiloxane polymers are certainly promising for future medical uses, especially for various medico-technological devices. PDMS is also an indispensable component for modifying other polymers.

7.4.2 Polyurethanes. Polyurethane materials have been intensively introduced into medical practice in the last decade, in view of their physico-chemical properties, which may vary over a wide range.

The polyurethane (PU) polymer chain involves the urethane group



—NH—C—O—, structurally close to the protein peptide group, this possibly being a determining factor in the successful use of this class of synthetic materials for bioplasty.

Items from segmented PU with ether bonds are used as thrombus-resistant materials, catheters, intra-aortal balloons and artificial heart parts.

Foam PU with ester bonds are traditionally used as adhesives and various alloplastic materials. Numerous investigations[35,110–113] have been devoted to problems of biocompatibility and biodegradation of PU alloplastics particularly of adhesive compounds.

The authors of Reference 113 conclude that the basic reaction is the hydrolysis of ester bonds, as a result of which PU adhesives and alloplastics degrade in the tissues of a living body. At the same time, these authors deny the involvement of enzymes in the degradation process, on basis of their model experiments using trypsin, chimotrypsin and elastase solutions, since in all cases enzymes did not appear to contribute to the degradation rates in these media or in a physiological solution as seen from the absence of changes in M_n, or in the intensity of the IR absorption bands.

It was noted above that in selecting the enzymes for in vitro experiments, one must use enzymes which are in the capsule of a given polymer. For instance, aminopeptidase and acid phosphatase were found in the PU capsule.[3] This helps understanding the negative effect reported in paper[113] for usual proteolytic enzymes that in many cases have an inhibitory effect. The kinetic data for PU with ester bonds showed that degradation occurs as a result of hydrolytic breaking of those bonds in the bulk under action of water, this being evidenced by change in M_n; on the other hand, the difference in destruction rates should apparently be explained by participation of enzymes in degradation from the surface of the polymer material in the random breaking reaction of urethane bonds, as shown for PGL.[62]

The degradation mechanism is different for segmented polyurethanes with different ratios of ether bonds, or for polydimethylsiloxane blocks which are used as thrombus-resistant materials that withstand the body medium.[29]

TABLE IX

Parameters of the biocompatibility and biodegradability of some polymers

Polymer	Biodegradability: Type of biodegradation and catalytical agents	Biodegradability: Lifetime	Biocompatibility: Toxicity class	Biocompatibility: Toxicity of the destruction products
Polycaproamide	$S_{(enz)}$, $V_{(salts)}$	On mass $m = m_0 - 1.6 \cdot 10^{-3}$ g/day $\cdot t$ lifetime for filament with diameter 24 ± 4 mkm in subcutaneous fat rabbit equal 500 + 50 days	1	moderate
Polydodecaneamide	$S_{(enz)}$, $V_{(salts)}$	On mass $m = m_0 - 1.1 \cdot 10^{-3}$ g/day $\cdot t$	1	moderate
Polyglycolide	$S_{(enz)}$, $V_{(salts,water)}$	Equation (17), p. 22 with values of the rate constants from Table VIII lifetime in the tensile strength in the subcut. fat rabbit equal 20–25 days	1	minimal
Polyglactine	$S_{(enz)}$, $V_{(salts,water)}$	Equations are analogy to PGL	1	minimal
Polyethylene therephtalate	$S_{(enz,salts)}$	On the mass $m = m_0 - 4.0 \cdot 10^{-1}$ g/sm^2 day$^{-1} \cdot t$ s lifetime on the tensile strength equal (30 ± 7) days for filament with diameter (19 ± 2) mkm (clinical date)	—	moderate
Polydimethylsiloxane	$S_{(water,enz)}$	On the mass $m = m_0 - 1.5 \cdot 10^{-5}$ g $\cdot$ sm^{-2} day$^{-1} \cdot t$ s	1	moderate
Polyethylene	$S_{(enz)}$	On the mass $m = m_0 - 2.1 \cdot 10^{-6}$ g $\cdot$ sm^{-2} day$^{-1} \cdot t$ s	—	—
Polypropylene	$S_{(enz)}$	—	—	—

7.5 Cyanoacrylate Adhesives

Adhesives based on alkyl-aryl α-cyanoacrylates are widespread in experimental and clinical surgery. An earlier review[114] outlines the basic results of using cyanoacrylate adhesives. According to many investigators, in the general case cyanoacrylate adhesives degrade at a considerable rate, depending on the length of the main chain and the nature of the radicals. Unfortunately, no quantitative data on degradation of adhesives are available.

CONCLUSION

In conclusion we have attempted to present the quantitative data on some polymer degradation in the living body as a "macrokinetical atlas" of the biodegradation summarised in the Table IX.

References

1. A. M. Tshernuhk, "Vospalenie," Moscow: Medicina, 1979.
2. B. Monis, T. Weinberg and G. J. Spector, *Br. J. Exp. Pathol.*, **49**, 302 (1968).

3. T. N. Salthous, *J. Biomed. Mater. Res.*, **10**, 197–229 (1976).
4. P. A. Ward, *Inflammation*, In: "Principles of Pathology," Ed. by M. F. Flavia and R. D. Hill, Univ. Press., Oxford-N.Y., 1971.
5. T. N. Salthous and B. F. Matlaga, *J. Surg. Res.*, **19**, 127 (1975).
6. R. E. Wilsnack, D. V. M. Bernadyn and B. S. Huntington, *Art. Org.*, **7**, 527 (1979).
7. K. de Dijuv, *Lyzosomy*, In: "Structure and Function of the Cell," Ed. by G. M. Frank, Moscow: Mir, p. 90, 1964.
8. G. D. Winter, *J. Biomed. Mater. Res.*, **5**, 11 (1974).
9. D. Bruck, *J. Biomed. Mater. Res.*, **11**, 1 (1977).
10. R. Lebaux, "Practical Toxicology of Plactica," London, p. 11, 1968.
11. W. L. Guess and J. Autian, *Am. J. Hosp. Pharm.*, **21**, 261 (1964).
12. R. M. Rice, A. F. Hegneli, C. W. R. Wade, J. G. Dilon, H. Jaffe and R. K. Kulkarni, *J. Biomed. Mater. Res.*, **12**, 43 (1978).
13. S. J. Courlay, R. M. Rice, A. F. Hegneli, J. G. Dilon, H. Jaffe and R. K. Kulkarni, *J. Biomed. Mater. Res.*, **12**, 219 (1978).
14. M. F. Nichols, *J. Biomed. Mater. Res.*, **13**, 299 (1979).
15. R. F. Wilsnack and D. V. M. Huntingdon, *Biomater. Med. Dev. Artif. Org.*, **4**, 235 (1976).
16. J. Rosenblath, *J. Pharmaceut. Sci.*, **54**, 156 (1965).
17. W. L. Guess and S. A. Rosenblath, *J. Pharmaceut. Sci.*, **54**, 1545 (1965).
18. R. I. Johnsson and A. F. Hegyyeli, *Ann. N.Y. Acad. Sci.*, **146**, 66 (1968).
19. A. Weninberg, G. Haselgren and L. Tronsted, *J. Biomed. Mater. Res.*, **13**, 109 (1979).
20. Yu. V. Moiseev and G. E. Zaikov, "Chemical Stability of Polymers in Aggressive Media," Moscow: Khimia, 1979.
21. M. Shen and M. B. Bever, *J. Mater. Sci.*, **7**, 741 (1972).
22. J. A. Barrie, "Diffusion in Polymers," Ed. by J. Grank and G. S. Park, London: Acad. Press, p. 259, 1968.
23. V. I. Lebedev, G. P. Andrianova and A. E. Tshalykh, "Diffuzionnye jiavlenia v polimerakh, Abstracts of 1 Meeting," Part 1, Riga, p. 323, 1977.
24. W. R. Vieth and K. J. Sladen, *J. Colloid. Sci.*, **20**, 1014 (1965).
25. W. R. Vieth, C. S. Frangoulis and J. A. Rionda, *J. Colloid. Sci.*, **22**, 454 (1966).
26. Z. A. Rogovin, E. I. Khait, I. L. Knunijnth and Ju. A. Rymaschevskaya, *Zh. Obshcei Khim.*, **17**, 1316 (1974).
27. V. A. Burschtein, L. M. Egorova and V. V. Solovijev, *Mekhanika polimerov*, **5**, 854 (1977).
28. A. A. Khokhlov, Dissertation, Moscow, 1980.
29. M. K. Shiystaleva, M. N. Kurganov and A. I. Tarakanov, *Mekhanika kompozitnykh materialov*, **5**, 34–42 (1985).
30. L. V. Ivanova, Yu. V. Moiseev and G. E. Zaikov, *Vysokomol. Soed., A*, **14**, 1057 (1972).
31. E. Laifut, "Yiavlenia perenosa v zhivykh sistemakh," Moscow: Mir, Vol. 18, p. 1, 1977.
32. A. L. Iordanskii and G. E. Zaikov, "Diffusion on Electrolytes in Polymers," VSP, Utrecht, 1988.
33. Yu. V. Moiseev, L. G. Privalova, T. T. Deurova, O. S. Veronkova and K. Z. Gumargalieva, Proceed. of the 17th Microsymp. on Macromolecule, Prague, p. 27, 1977.
34. K. Z. Gumargalieva, Yu. V. Moiseev, T. T. Daurova, O. S. Veronkova and I. B. Rozanova, *Biomaterials*, **1**, 215 (1980).
35. E. A. Lipatova and G. A. Pkhakadze, In: "Application of the Polymer in the Surgery," Kiev: Naukova Dumka, p. 7, 1977.
36. G. E. Zaikov, *International Journal of Polymeric Materials*, 3–8 (1994).
37. S. Ja. Karpukhina, K. Z. Gumargalieva, V. M. Mironova and T. T. Daurova, *Vysokomol. Soed.*, **25B**, 209–212 (1983).
38. D. F. Williams, Proceed. of ASTM Conference, Kansas City, ASTM Special Publ., B. Syrett and A. Acharya, 1979.
39. D. F. Williams, *J. Biomed. Mater. Res.*, **14**, 329 (1980).
40. R. Smith and D. F. Williams, *J. Biomed. Mater. Res.*, **21**, 991–1003 (1987).
41. D. V. Park, "Biokhimia chuzherodnykh soedinenii," Moscow: Medicina, 1978.
42. D. F. Williams and P. Roaf, "Implants in Surgery," Moscow: Medicina, 1978.
43. K. Schwertassek, *Faserforcsh. and Textiltechn.*, **11**, 125 (1960).
44. O. S. Voronkova and T. T. Daurova, *Vysokomol. Soed., A*, **13**, 677 (1971).
45. Yu. V. Moiseev, V. S. Markin and G. E. Zaikov, *Uspekhi Khimii*, **45**, 510 (1976).
46. G. E. Titova, Abstracts Proceed. Meeting "Polymers in Medicine," Leningrad, 1975.
47. G. E. Titova and M. S. Akutin, "Modification of the Polyamide-12 Layer," Plasticheskie massy, vol. 1, p. 73, 1976.
48. G. E. Titova, "Polyamide-12 Stability in the Living Body," Dissertation, Moscow, 1976.
49. D. Heikens, *J. Pol. Sci.*, **35**, 277 (1980).

50. D. F. Williams, *J. Mater. Sci.*, **17**, 1233–1246 (1982).
51. C. C. Chu and G. Momcrief, *Ann. Surg.*, **198**, 223 (1983).
52. T. P. Nuquid, *Phyllip J. Surg.*, **21**, 215 (1969).
53. Y. Chuja, K. Suchiro, H. Todokoto and K. Chuio, *Macromol. Chem.*, **103**, 215 (1968).
54. K. Chuio, H. Kobayaski, J. Suzuki and S. Tokuhara, *Macromol. Chem.*, **100**, 267 (1967).
55. H. Zilch and W. Kleengel, *Die Schwester*, **10**, 34 (1971).
56. A. M. Reed and D. K. Gilding, *Polymer*, **22**, 494 (1981).
57. J. M. Brady, D. E. Gutright, R. A. Miller, G. S. Battistone and E. E. Hunsuck, *J. Biomed. Mater. Res.*, **7**, 155 (1973).
58. D. E. Cutright and E. E. Hunsuck, *Oral. Surg.*, **31**, 134 (1971).
59. D. E. Cutright, E. E. Hunsuck and J. D. Brady, *J. Oral. Surg.*, **29**, 39 (1971).
60. C. C. Chu, *J. Appl. Polym. Sci.*, **126**, 1727 (1981).
61. C. C. Chu, *J. Biomed. Mater. Res.*, **15**, 19 (1981).
62. Yu. V. Moiseev, T. T. Daurova, O. S. Voronkova, K. Z. Gumargalieva and L. G. Privalova, *J. Polymer. Sympos.*, **66**, 269 (1979).
63. L. L. Razumova, T. T. Daurova, A. A. Veretennikova, L. G. Privalova and K. Z. Gumargalieva, Polimery v medicine, **9**, 119 (1979).
64. L. G. Privalova, K. Z. Gumargalieva, O. S. Voronkova, Yu. V. Moiseev, T. T. Daurova, L. L. Razumova and G. E. Zaikov, *Vysokomol. Soed., A*, **22**, 1891 (1980).
65. J. Herman, R. I. Kelley and G. A. Higgins, *Arch. Surg.*, **100**, 486 (1970).
66. J. D. Bankroft, "An Introduction to Histochemical Technique," New York: Appleton Century Crofts, 1967.
67. R. K. Kulkarni, E. G. Moore, A. F. Hegueli and F. Leonard, *J. Biomed. Mater. Res.*, **5**, 169 (1971).
68. P. H. Craig, J. A. Williams, A. D. Macoun, *et al.*, *Surg. Gynecol. Obstet.*, **141**, 1 (1975).
69. T. N. Salthous, G. K. Kaminska and M. L. Murphy, "Suture Absorption in Rabbit Cornea and Sclera," *Invest. Ophthalm.*, **9**, 884 (1970).
70. C. C. Chu and N. D. Campbell, *J. Biomed. Mater. Res.*, **16**, 417 (1982).
71. R. M. Robert, J. M. Brady and D. E. Cutright, *J. Biomed. Mater. Res.*, **11**, 711 (1977).
72. T. N. Salthous and B. F. Matlaga, *Surg. Gynecol. and Obstetrics*, **141**, 544 (1976).
73. K. Schwertassek and J. Dvorak, *Faserforsch. und Textiltechnik.*, **24**, 115 (1970).
74. K. Schwertassek and J. Dvorak, *Textil, Praha*, **26**, 196 (1971).
75. K. Schwertassek and J. Dvorak, *Faserforschung und Textiltechnik*, **23**, 2 (1972).
76. H. H. Harison, *Am. J. Surg.*, **95**, 3 (1968).
77. R. W. Postlethwait, *Ann. Surg.*, **171**, 892 (1970).
78. R. W. Postlethwait, *Ann. Surg.*, **10**, 759 (1976).
79. Y. Noishica, *J. Biomed. Mater. Res.*, **10**, 759 (1976).
80. T. T. Daurova and S. M. Degtijareva, *Bullet. Eksperim. Biol. i. medic.*, **64**, 366 (1977).
81. T. T. Daurova, *et al.*, *Doklady Akad. Nauk.*, **231**, 919 (1976).
82. T. E. Rudakova *et al.*, *J. Pol. Sci., Polymer. Symp.*, **66**, 277 (1979).
83. K. Z. Gumargalieva, Yu. V. Moiseev, T. T. Daurova and O. S. Voronkov, *Biomaterials*, **3**, 177 (1982).
84. Z. A. Rogovin, "Osnovy chimii i tekhnologii volokon," Moscow, p. 140, 1964.
85. D. A. Ravens, *Polymer*, **1**, 375 (1960).
86. J. V. Maxham and W. J. Maier, *Biotechnol. and Bioeng.*, **20**, 865 (1978).
87. T. C. Liebert, R. P. Cherthoff, S. L. Cosgrofe and R. Mc. Cuskey, *J. Biomed. Mater. Res.*, **10**, 939 (1976).
88. T. I. Vinokurova, I. B. Rozanova and S. M. Degtijareva, Proceed. 3rd Symposium on Polymers in Medicine, Belgorod-dnestrovskii, p. 112, 1977.
89. J. Dolezel, *Plasty a kaucuk*, **13**, 257 (1976).
90. O. V. Startsev, A. L. Iordanskii and G. E. Zaikov, *Polymer Degrad. and Stability*, **18**, 412–418 (1987).
91. S. N. Levins, *Ann. New York Acad. Sci.*, **146**, 3 (1968).
92. Ann-Christine Albertson, Sven Ove Andersson and Sigbritt Karlsoon, *Polymer Degradation and Stability*, **18**, 73–87 (1987).
93. N. E. Stinson, *J. Exper. Pathol.*, **46**, 135 (1965).
94. J. Charnley, A. Kamangar and M. D. Longfield, *Medical and Biol., Engin.*, **7**, 31 (1969).
95. N. M. Emanuel and Yu. N. Lijaskovskaija, "Tormozhenie processov okisleniia pishevykh zhirov," Moscow: Pischepromizdat, 1961.
96. N. B. Nykvist, *Plastic Polymers*, **42**, 195 (1974).
97. I. P. Fischer *et al.*, "First Biomaterials Congress," Baden near Vienna, Austria, p. 223, 1980.

98. M. Mlinac and I. Munjko, The 2nd Intern. Symp. on Biodegradation and Stabilization of Polymers, Dubrovnik, 1978.
99. A. S. Albertson and B. Ranby, Proceed. 3rd Inter. Biodegrad. Symp., Kingston, Rhode Island, p. 743, 1975.
100. Robert A. Miller, J. M. Brady and D. E. Cutright, *J. Biomed. Mater. Res.*, **11**, 405 (1977).
101. G. E. Zaikov, *J. Macromol. Sci. Rev.*, *C*, **25**, 551–597 (1985).
102. E. J. Frazz and E. E. Schmidt, *J. Biomed. Mater. Res.*, *Sympos.*, **1**, 43 (1973).
103. N. I. Ostrethova, Dissertation, Moscow, 1980.
104. W. F. Agnew, E. M. Todd, H. Richmond and W. S. Chronister, *J. Surg. Res.*, **2**, 357 (1963).
105. N. I. Ostrethova and A. N. Neverov, *Vysokomol. Soed.*, *B*, **16**, 55 (1974).
106. N. I. Ostrethova, T. T. Daurova and A. N. Neverov, *Polimery v medicine*, **6**, 122 (1976).
107. M. G. Voronkov, "Geterothiklicheskie reakthii rassheplenija siloksanovych svijazei," Moscow: Khimia, p. 123, 1961.
108. D. K. Thomas and B. B. Moor, *Polymer.*, **13**, 109 (1972).
109. I. A. Metkin, K. K. Piotrovskii and Iu. A. Iuzhelevskii, *Zhurnal prikladnoi khimii*, **48**, 1108 (1975).
110. J. W. Boretos, W. S. Pierse, R. E. Baier, A. F. Leroy and H. I. Donachy, *J. Biomed. Mater. Res.*, **9**, 327 (1975).
111. N. A. Plate and L. I. Valuev, *J. Vsesouzn. Khimich. Obchestva im. Mendeleeva*, **30**, 402–410 (1985).
112. H. Hernauer, *Plaste und Kautschuk*, **10**, 413 (1963).
113. T. E. Lipatova, T. T. Alekseev and T. L. Tereshenko, *Polimery v Medicine*, **10**, 19 (1980).
114. G. A. Pkhakadze, E. A. Tereshenko, N. A. Galatenko and A. K. Kolomiitsev, *Biocompatability*, **1**, 33–42 (1993).
115. W. Lemm, Ed. by H. Plank, G. Egbers and I. Sgre, "Biodegradation of Polyurethans, Polyurethans in Biomedical Engineering," Elsevier Sci., Publ. B. K., Amsterdam, pp. 103–108, 1985.
116. T. E. Lipatova and G. A. Pchakadze, "Medical Adgezive," Kiev: Naukova Dumka, 1979.