Kinetics and mechanism of biodegradation of (co)polyglycolide sutures

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SUMMARY: Biodegradation *in vivo* of modified and unmodified PG (polyglycolide) and PGL (copolymer glycolide - L - lactide) monofilament sutures were studied using ^{1}H- NMR, wide and small angle X-ray scattering, differential scanning calorimetry (DSC), electron microscopy (EM), Fourier transform (FT) Raman spectroscopy methods. It was found that the process includes a steady-state and accelerated stages of biodegradation. The suture biostability depends on polymer morphology changing widely over the suture draw ratio. The modification of polymer chain results in an increase in suture useful lifetime without significant changes of complete polymer degradation time. It was also established the important role of weak intermolecular hydrogen bonds such as CH---O=C in the suture stability.

Introduction

The main advantages of biodegradable synthetic materials over those of natural origin include the known, predictable composition and the control of useful life time, the both factors are of the particular importance for biomedical devices. The synthetic polyesters of glycolic acid (polyglycolide PG), lactic acid (polylactide) and their copolymers combining the good mechanical properties, the biocompatibility with the inherent for human body destruction products are of special interest for various biomaterials such as sutures, osteosynthetic devices, etc. and also are considered as a potential materials for drug carriers. To develop new biodegradable materials with predetermined properties, and with adjusted useful in vivo lifetime especially, the understanding of biodegradation process on molecular level is of primary importance.

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Results and discussion

The biodegradation of modified and unmodified PG and PGL monofilament sutures with different draw ratio (λ) were studied. The one of the most attractive feature of these materials is a fast and complete in vivo degradation of polymer residues in 120 days for PG and in 90 days for modified PG and PGL sutures[1,2]. The modified PG and PGL were obtained by copolymerization of glycolide and/or glycolide-lactide 90/10 mixture with hydroxyl terminated macromonomer such as monoester of polyoxyethylene glycol and alifatic acid, namely polyoxyethylene glycol monolaurat ($R=C_{11}$), with AB block copolymer formation, as was proven by ^1H - NMR-method.

The filaments were spun from polymer melt and then the fibers were drawn at 100°C to the different draw ratios and annealed. Studies on degradation of monofilament sutures were carried out in vivo.

As follows from Fig.1, the modification of PG and PGL results in the considerable increase in monofilament suture tensile strength and in its retention in vivo suture degradation (a', b') comparing to those characteristics of unmodified polymers (a, b). The degradation process involves two stages as seen in Fig.1 (curves b and b') and in Fig.2: at the initial stage the degradation rate and corresponding rate of the tensile strength loss ($-d\sigma/d\tau$) - is the constant, later on the process accelerates with progressively increase in $-d\sigma/d\tau$ value.

According to ^1H- NMR study of polymer residues solutions in d^6 - DMSO, at the initial stage of unmodified PG sutures degradation in vitro the backbone cleavage via ester group hydrolysis occurs in the lower molecular weight polymers 1 with hydroxyl (~$\underline{CH_2}$-OH, δ =4,12 p.p.m.) and carboxyl ((~$\underline{CH_2}$-C(O)OH, δ=4,64 p.p.m.) terminal groups formation (Fig.3, a). At the later stages the mobile low molecular weight products such as diglycolic 2 (~$\underline{CH_2}$-OH, δ= 4,09 and ~$\underline{CH_2}$-C(O)OH, δ=4,59 p.p.m) and glycolic acids 3 (δ=3,93 p.p.m.) (Fig.3 b) appear. Their diffusion in suture volume and in surrounding medium leads to the significant acceleration of the further biodegradation. The possible reaction scheme is shown below.

$$-[O\text{-}CH_2\text{-}C(O)O\text{-}CH_2\text{-}C(O)]_n\text{-} + H_2O \rightarrow H\text{-}[O\text{-}CH_2\text{-}C(O)O\text{-}CH_2\text{-}C(O)\text{-}]_n\text{-}OH \rightarrow$$

$\rightarrow$ HO-CH_2-C(O)-O-CH_2-C(O)-OH + HO-CH_2-C(O)-OH

2 3

This model is supported by results of pH changes of media at PG fibers degradation in distilled water[3].

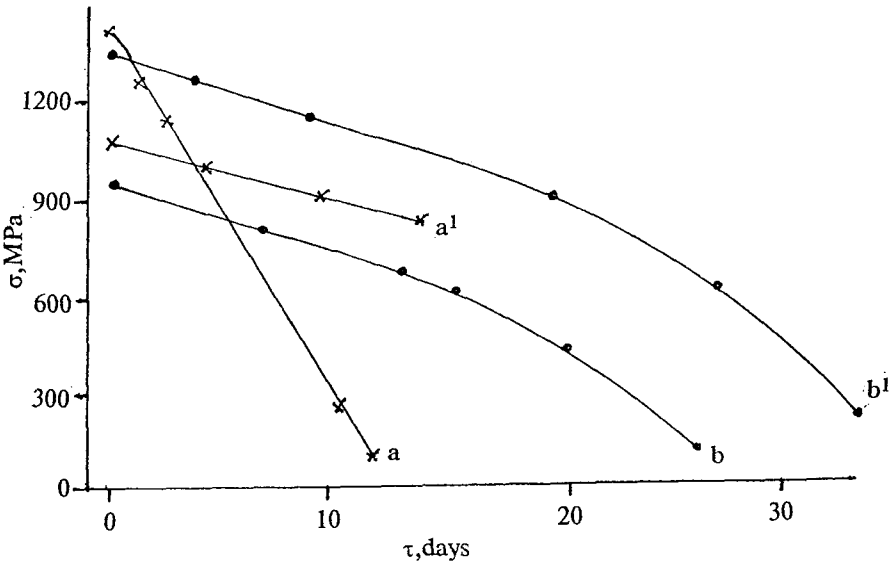

Fig.1.The tensile strength dependence σ on degradation time τ in vivo of modified (a',b') and unmodified (a,b) PG (a',a) and PGL 90/10 (b',b) monofilament sutures (λ≈5).

The structural changes at degradation in vivo of the isotropic pellets and drawn fibers of unmodified (PG-1) and modified (PG-2) were studied by small and wide angle X-ray scattering methods. It was shown that the long period corresponding to the distance between adjacent crystallites decreases after several days of biodegradation with significant increase in intensity of small angle maximum. (Table 1). Such changes can be interpreted as destruction of amorphous regions, leading to enhancement of electron density difference between phases, besides that the extended molecules passing from one crystallite to another relax, shrink and appropriate decrease in long period is observed.This process is dominant at the first stage of degradation.

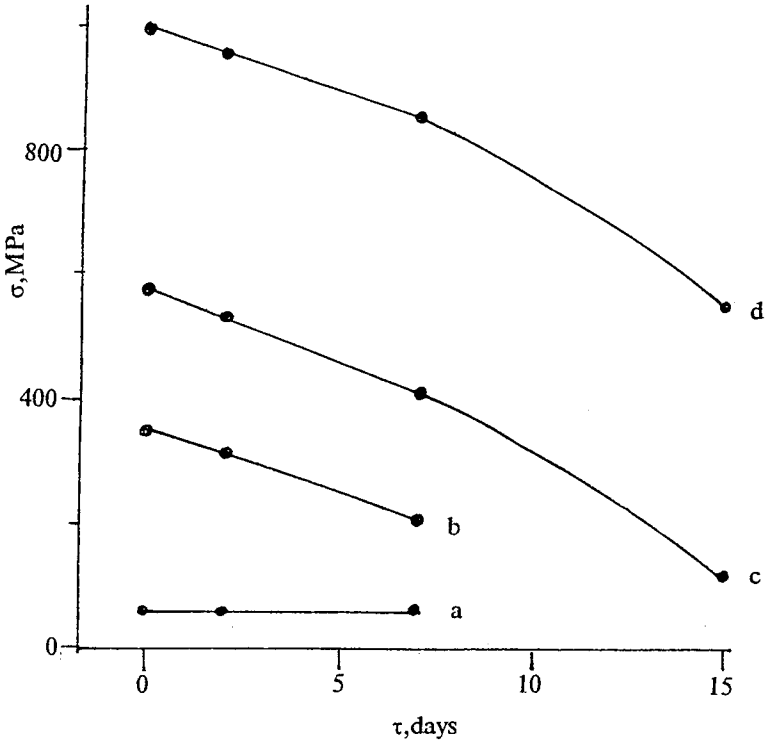

Fig.2. The tensile strength σ dependence on degradation time τ in vivo of modified PG monofilament sutures with different draw ratio: as-spun - (a), λ = 3 (b), 4 (c), 5 (d)

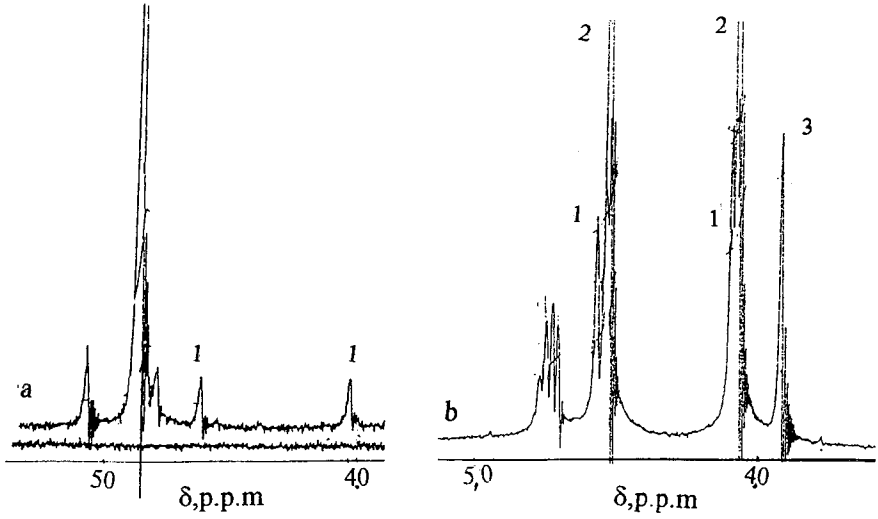

Fig.3. ^1H - NMR spectra of degradation products of unmodified PG sutures at different stages of in vitro degradation, H_2O, t=25^0 C: a) the initial stage; b) the final stage (d^6 - DMSO solution, t= 120^0 C).

The substantial change of lateral crystallite size takes places only after 18 days of in vivo degradation in the case of the isotropic unmodified (PG-1) and modified (PG-2) pellets (Table 1). It means at the later stage the significant destruction starts in crystalline regions as well.

The suture tensile strength loss during biodegradation corresponds to the increase of total crystallinity of sutures as follows from the DSC data. The crystallinity of unmodified PG-1 suture (λ=4,4) increases from 0,36 to 0,55 (Fig. 4). Such behavior can be understood in terms of the continuous decrease of amorphous phase volume fraction as was suggested based on SAXS data (Tabl.1) and/or due to the crystallization of oligomers formed during degradation or due to recrystallization process caused by plasticizing effect of environment. It should be noted that the limit suture crystallinity of 0,55 achieved after ~12 days in vivo corresponding to complete amorphous layer degradation, to the total tensile strength loss and suture fragmentation.

Tab.1. Changes of structural parameters: lateral crystallite size l_{020} and long period L of isotropic samples* (pellets) and monofilament sutures** with different draw ratio λ of unmodified PG-1 and modified PG-2, respectively, as a function of degradation time τ in vivo

	l (020), Å			L, Å				
τ, days	PG-1*	PG-2*	τ, days	PG-1**		PG-2**		
				λ=1	3	λ=1	3	5
0	165	162	0	135	108	113	100	99.7
18	95	114	2	94.6	98.4			
25	91	102	6			91.4	82	82
29	96	93						
36	94	92						

The additional evidence of the predominant amorphous phase degradation follows from the electron microscopy data (EM). After 20 days of degradation in vivo the unmodified PGL suture contains the macrofibrils surrounded by dense shell of a less degradable polymer, as was also described elsewhere[4], with the full absence of interfibrillar amorphous regions (Fig 5).

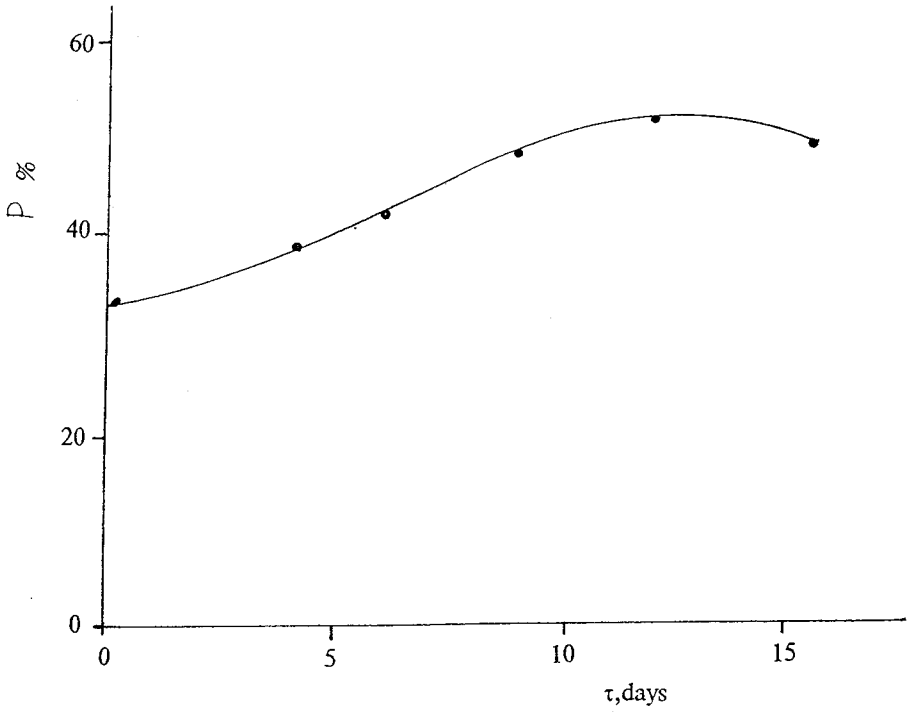

Fig.4. The change in the crystallinity P as a function of in vivo biodegradation time τ for unmodified PG monofilament sutures .

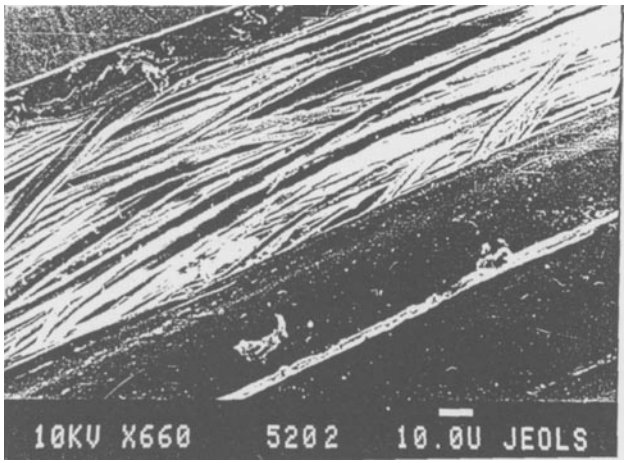

Fig.5. EM of unmodified PGL monofilament suture (λ= 4,4) after biodegradation in vivo: τ =20 days.

Concerning the influence of a suture draw ratio on its stability in vivo one can conclude that the suture useful life time, the period of constant degradation rate as well as suture initial tensile strength increases with λ, and the degradation rate (- dσ/ dτ) is a linear function of λ (Fig. 6) decreasing with the increase of draw ratio. This effect is connected in our opinion with the supramolecular structure of drawn PG fiber, particularly with the increase of amorphous regions density and appropriate changes in mass transport properties of material.

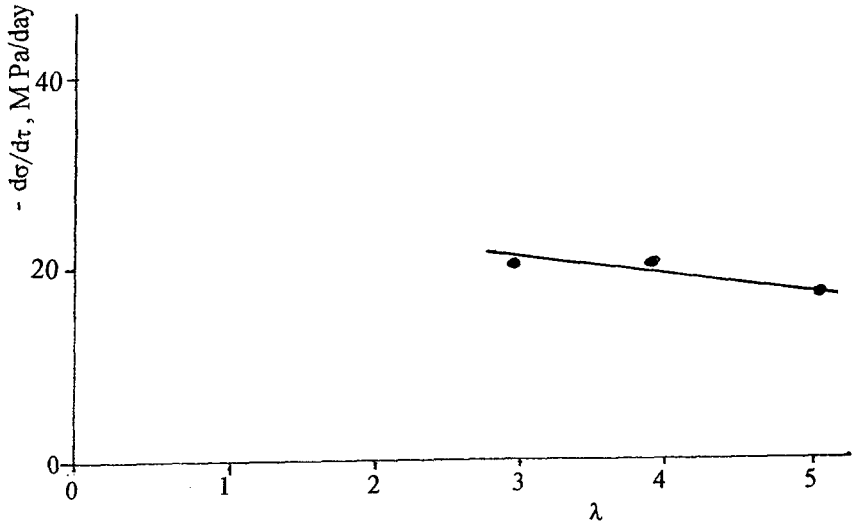

Fig.6. The tensile strength loss rate (biodegradation rate) - dσ / dτ in vivo of monofilament modified PG sutures as a function of draw ratio λ.

The drawing of studied fibers is accompanied by the transition from lamellar to dense fibrillar supramolecular structure with high number of inter- and intrafibrillar tie molecules connecting the adjacent crystallites. The increase of λ leads to unfolding of molecules, to tie chains (TM) extension, orientation and transition in taut tie molecules (TTM) and to a rise in the fraction of impermeable TTM in amorphous layers. The high alignment of chains in microfibrils and in interfibrillar amorphous regions leads to higher amorphous density and to the observed decrease of transport properties. Similar effect of draw ratio was observed at studies on the mass transport properties of methylene

chloride [5] in the polyethylene fibers, where sorption and diffusion coefficient D_0 decreased sharply with drawing. For polyethylene D_0 is a linear function of λ up to λ_c =8 - 9 and then dropped drastically to ~1 / 200 of the initial value, at the same time the sorption decreased in seven times which corresponds to complete transformation of the easily permeable lamellar structure into an almost impermeable to the penetrating molecules microfibrils[5] .

Similarly, the low diffusion coefficient and high density of highly drawn PG fibers affect their degradation. The following observed experimental results testify in behalf of proposed model:

1) suture initial tensile strength increases linearly with λ;

2) change of long period together with the decrease of small-angle maximum intensity at the drawing show the densification of amorphous regions (Fig.7) due to the rise of the number of taut tie molecules in there. Similarly, the increase in crystallinity according to DSC data (Fig.8) during drawing can be explained not only by thickening of the crystalline blocks but also and mostly by the contribution of extended and oriented chains of the amorphous regions[9];

3) the polymer melting peak shifts to higher temperature with drawing: from t = 217,4^{0}C (λ=3) to t = 221^{0}C (λ =5) for PG-2 as it follows from DSC data indicating the perfection of crystalline structure.

4) EM data (see Fig. 5) clearly demonstrated a microfibrillar structure of PGL unmodified suture at the limit draw ratio λ = 5,3 , t= 100^{0}C.

The direct relationship between the molecular orientation and the suture biostability was obtained from "dichroic" Fourier transform (FT) Raman measurements of PG-2 samples with different draw ratio. As is seen in Fig.9 and Fig.10 the chain orientation in "isotropic" sample (pellet) of lamellar structure[6] and in a "as-spun fiber" is practically the same, while in suture with the maximum draw ratio (λ =5,1) the "dichroic" ratio is much higher in a good agreement with the data for biodegradation of sutures with different λ (see Fig. 2, a, d and Fig.6). Thus the obtained data on dichroic ratios support the proposed above transition from isotropic lamellar to highly oriented fibrillar morphology.

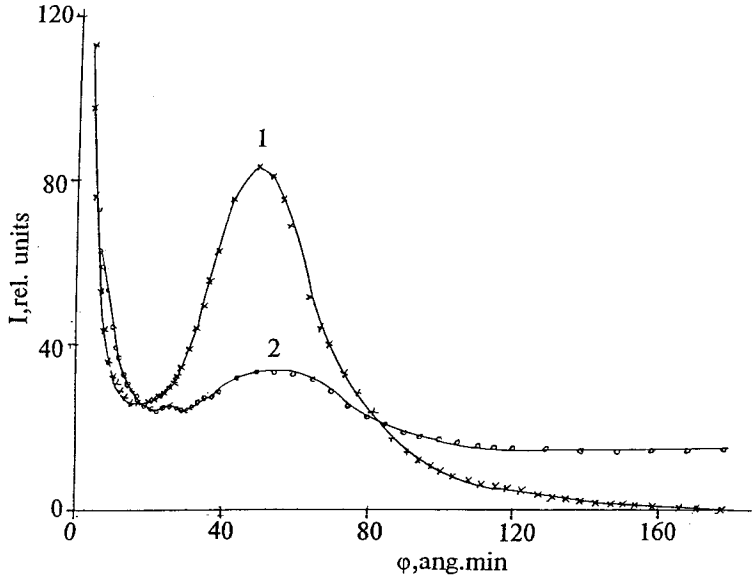

Fig.7. Meridional distribution of small angle X-ray scattering intensity I by monofilament modified PG sutures with different draw ratios λ: λ = 3 (1), 5 (2).

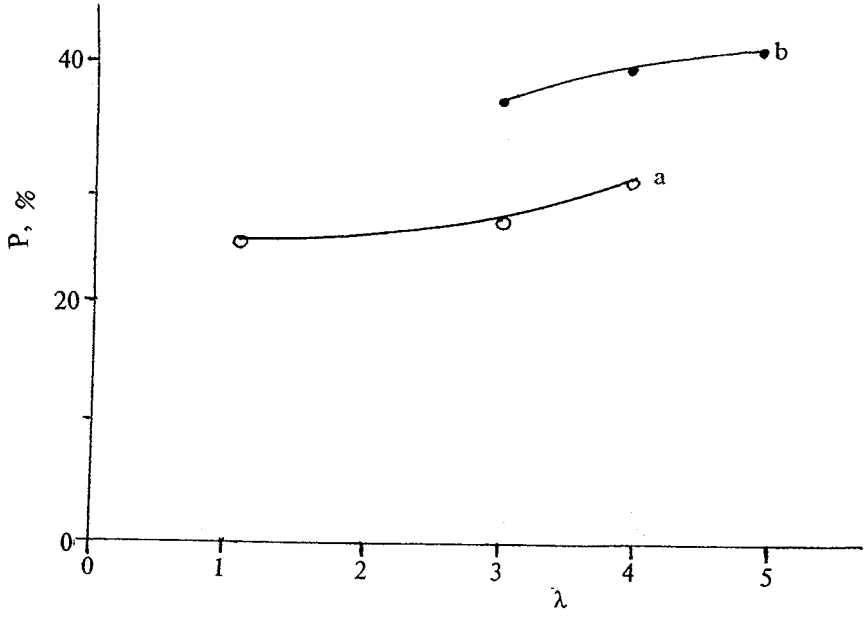

Fig.8. The crystallinity P of unmodified (a) and modified (b) monofilament PG sutures as a function of draw ratio λ from DSC data.

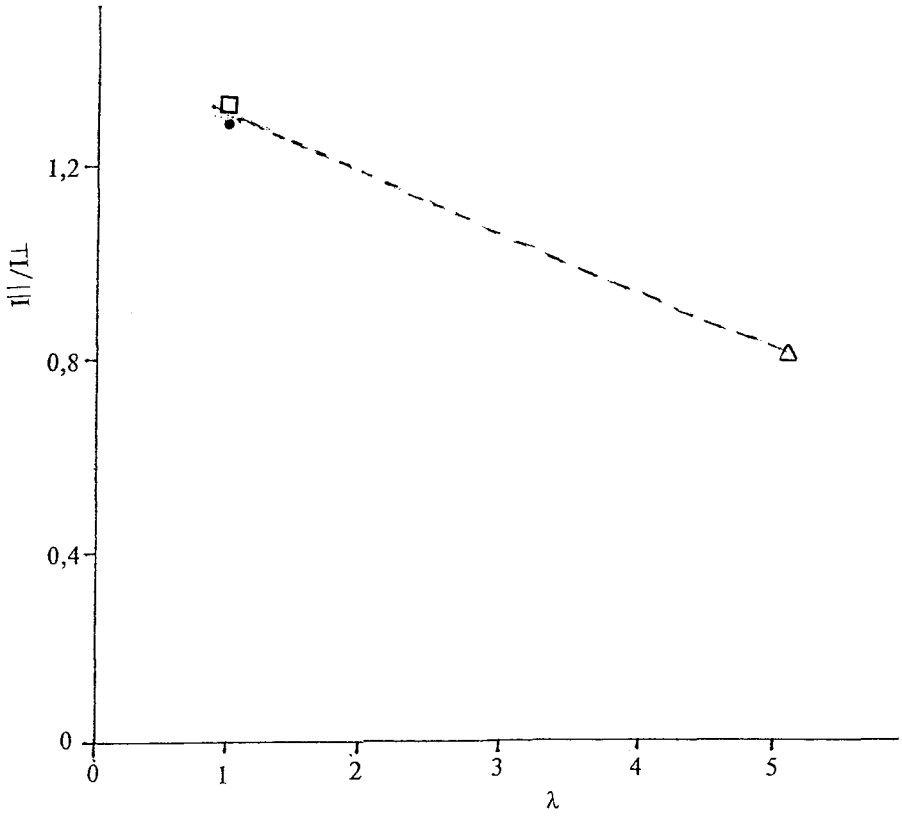

Fig.9. "Dichroic ratio" $D = I_{||} / I_{\perp}(\nu_{C=O})$ as a function of draw ratio λ of modified PG: isotropic sample (pellet) λ=1 •, "fiber as spun" λ=1 □ and high drawn suture λ=5.△.

A decrease of the suture permeability with drawing is connected also to the increase of a fraction of intermolecular interactions with carbonyl group ~C=O participation (see Fig.10, band at ν=1758 cm^{-1}, intensity of which grows with λ). As follows from X-ray analysis, the glycolide and lactide molecules are bound in crystals by weak CH---O=C hydrogen bonds [7]. The corresponding bands at 1758 and ~1750 cm^{-1} in glycolide Raman and FT IR spectra can be seen as a shoulder of the main C= O bands at 1770 and 1774

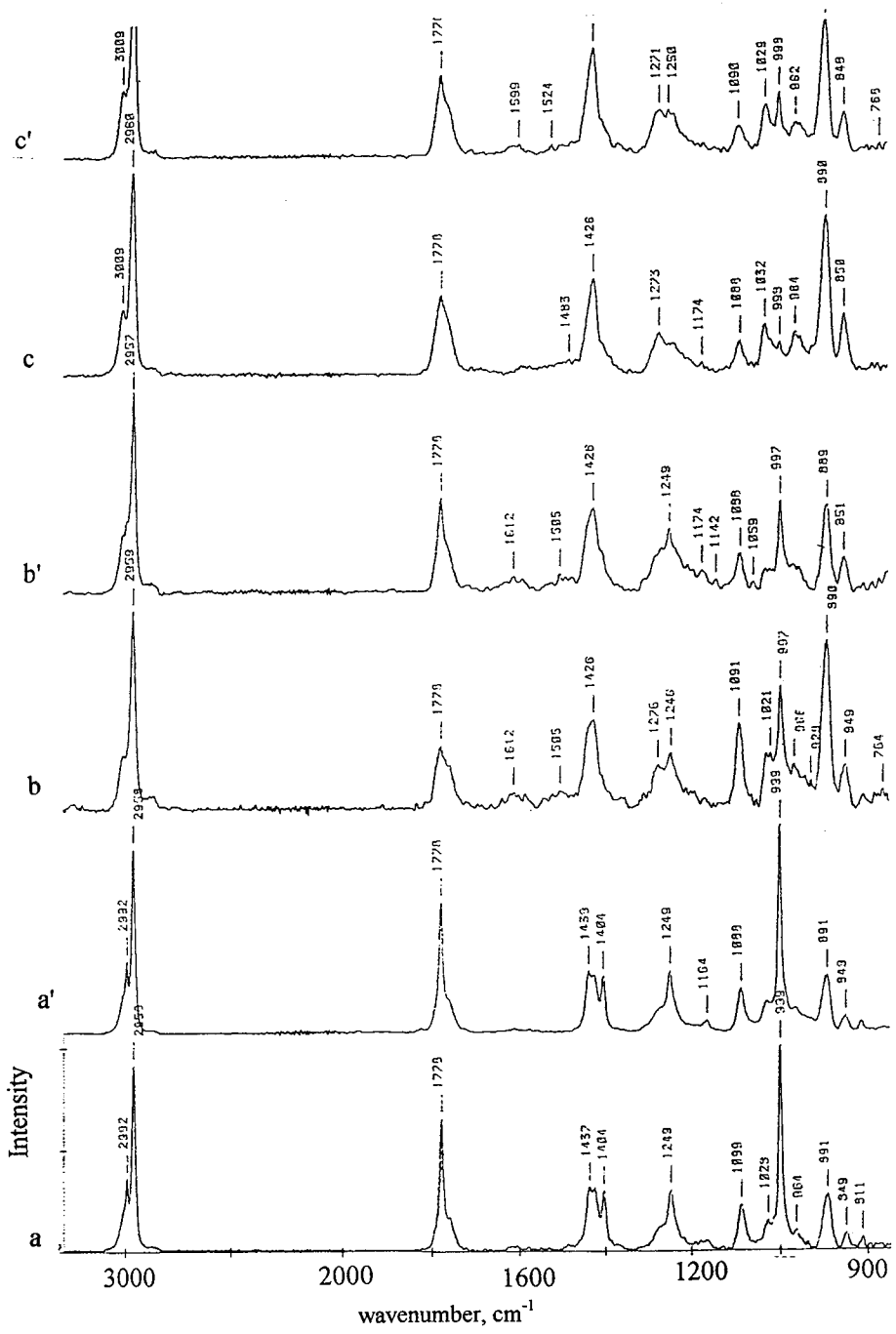

Fig.10. FT Raman measurements on modified PG: isotropic sample (pellet) (a,a') , "fiber as spun" (b, b') and high drawn suture λ=5 (c, c'). Spectra recorded in two ways - analyzer vertical (a,b,c) or horizontal polarized vertically (a',b',c').

cm^{-1} , respectively. The length of C--O=C spacing in glycolide (G) is very similar to that in polyglycolide (PG) fibers defined by neutron crystallographic analysis [8] (l_G= 3,104 Å[7] and l_{PG}= 3,29 Å[8], for d,l-lactide l = 3,202 Å[7]) which permits to assign such intermolecular interactions in PG to weak hydrogen bonds also. The formation of hydrogen bond network leads to more ordered polymer structure, and as result to hindering the access of media and retarding of suture degradation. Furthermore the decrease of vacant sites of carbonyl groups due to increase of intermolecular hydrogen bonding also inhibits the process.

As was already mentioned the modified PG and PGL sutures are significantly more stable to degradation in vivo as compared to unmodified ones.(see Fig.1). Lateral crystallite sizes in copolymer samples decreases slower on the early stages of degradation. The supramolecular structure of PG and PGL: long period (Table 1), crystallinity (Fig.8), etc., is quite different also. As was discussed above, the modified chains act as a lubricant promoting the chain sliding along each other, leading to their extension and alignment and to the formation of more closely packed structure resulting in the higher crystallinity of copolymer samples and their high biostability. Even more, the presence of the modified chains involved hydrophobic fatty acid blocks excluded to amorphous phase can decrease the media penetration into the suture volume considerably.

It should be stressed that complete destruction of unmodified and modified suture residues in vivo is almost the same (~90 days).

Conclusions

Studies on biodegradation in vivo of modified and unmodified polyglycolide and glycolide-lactide copolymer sutures by different instrumental methods, reveal that the process occurs at first in amorphous polymer regions and includes two stages: steady state and "accelerated" one. Biodegradation kinetics of the process is determined by special polymer morphology determined by transformation of lamellar structure to closely packed microfibrills at suture drawing which limits medium penetration into suture volume and retards the process. Furthermore, the increase of the suture draw ratio resulted in polymer high chain orientation along to the draw direction and in high level of interchain weak hydrogen bonding of CH---O=C, which also favors to the dense structure formation. Introduction of chemically bonded modificator into polyglycolide chain promotes the transformation process and leads to vastly enhance of suture tensile strength retention times.

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