Long term biodegradation *in vitro* of poly(ether urethane urea): a mechanical property study

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The effect of *in vitro* exposure to enzymatic and aqueous environments on the performance of poly(ether urethane ureas) (PEUUs) was studied. Stabilized and unstabilized PEUU samples were treated with papain, distilled water, or activating agent solutions. Durations of treatments were two weeks and one month. Treated and untreated samples were subjected to tensile and fatigue testing. A significant decrease in fatigue lifetime and ultimate tensile stress was observed in unstabilized PEUUs with two weeks and one month aqueous and enzymic treatments. For samples treated for one month with papain, optical microscopy indicated a change in the microdeformation mechanism of the PEUU elastomer from micronecking to crazing. The addition of stabilizers in the PEUU eliminated the loss in mechanical performance in all aqueous environments but was not effective against enzymatic degradation.

(Keywords: poly(ether urethane urea); degradation; infra-red spectroscopy; mechanical properties; enzymatic degradation; fatigue lifetimes; ultimate tensile stress)

INTRODUCTION

Segmented poly(ether urethanes) have been used widely and researched in the biomedical field since the 1960's, when they were shown to be excellent materials for biomedical use[1,2]. It is generally accepted that the excellent mechanical properties of segmented polyurethanes are primarily due to the phase separation of soft and hard segments leading to the formation of hard-segment domains which are dispersed in the rubbery polyether matrix. Chemical factors such as composition, molecular weight of the soft segment, length of the hard segment, and physical factors such as the fabrication method are used to alter the structure and morphology of phase separation in bulk or on the polymer surface. These factors, in turn, determine the performance in biomedical applications[3-5].

Many studies have been carried out on the mechanical properties of polyurethanes in order to relate these properties to the chemical and physical structures of the materials. In the linear elastomers, the hard segments serve as physical crosslinks and result in a stiffening of the material, i.e. increase the modulus[3-7]. During extension (100% to 300%) of the sample, the hard domains tend to align themselves toward the stretching direction, causing irreversible stress-softening. Thus, the amount of energy dissipation in the first one or two hysteresis loops depends upon the composition of the block polymer and increases with increasing hard segment concentration[8,9].

The primary concern of this study is the effect of biodegradation on the mechanical performance of polyurethane elastomers, especially the effects of an *in vivo* or *in vitro* physiological environment. When a polymeric material is implanted, it provokes an inflammatory response, including the migration and proliferation of various cells which synthesize, utilize and release various types of lysosomal enzymes[10,11]. The enzymes which are highly efficient catalysts may alter the chemical stability of the implanted material. The postulated role of lysosomal enzymes *in vivo* in polymer degradation is to reduce the activation energy of the chemical reactions. Thus, a degradation process that usually only takes place at elevated temperatures in the presence of oxygen or ultra-violet may occur in the enzymatic environment of the body[12].

Enzymes also have been found to degrade polymers *in vitro* when the enzyme is not specific to the chemical bonds which are broken. For example, polyamino acids are found to be degraded by proteolytic enzymes[13,14]. In recent work, the plant thiol endopeptidase, papain, which has broad specificity, has been utilized *in vitro* as an analogue of cathepsin B which is released by the cells of an acute and chronic inflammatory response[15]. Owing to its broad substrate specificity, papain has been suggested to be able to degrade the urea and urethane linkages of polyurethanes[15,16].

The work presented here was carried out to evaluate the effect of papain mediated degradation of PEUUs on mechanical performance. Fatigue and tensile tests were used to study mechanical changes caused by *in vitro* treatments. The effects of treatment on the PEUU chemistry have been reported elsewhwere[17]. Optical microscopy was used to study the microdeformation behaviour of both treated and untreated PEUU samples.

EXPERIMENTAL

Materials

Three kinds of solution grade films, stabilized (**I** and **II**) and unstabilized, were synthesized and fabricated into films by Mercor, Inc., Berkeley, CA, USA.

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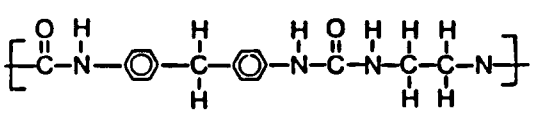
Poly(tetramethylene glycol) (PTMG) ($\bar{M}_n = 2000$) was reacted with diphenylmethane-4,4'-diisocyanate (MDI), and then chain extended using ethylene diamine in dimethylacetamide (DMAC). The generalized structure of a PEUU is shown in *Figure 1*. The molar ratio of PTMG, MDI and ethylene diamine was 2.5:3.5:1.0. Films (0.1 mm thick) were prepared by web coating filtered PEUU/dimethylformamide solutions on clear Mylar. The film was water extracted at 60°C for 24 h to remove any residue solvent. The complete removal of residual solvent was confirmed by infra-red analysis. Stabilizer I was 0.83% Santowhite/0.21% Tinuvin 328, and stabilizer II was 0.5% UV 3346/0.5% Tinuvin 328. Santowhite (hindered bisphenol) is an antioxidant which acts as a radical chain terminator. Both Tinuvin 328 (substituted benzotriazole) and UV 3748 (hindered amine) are u.v. absorbers. All three stabilizers are available from the Monsanto Corp., Akron, OH, USA.

Treatment conditions

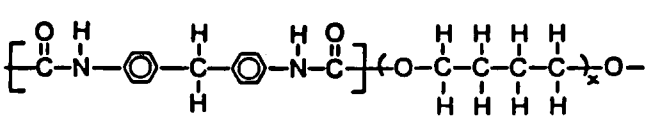
PEUU film samples were cleaned by sonication in distilled water for 15 min before any treatment or testing. Samples were treated by immersion in one of the following media: papain (two conentrations) solution, enzyme activating agent solution, or distilled water at room temperature. Samples in treatment media without papain and untreated samples provided experimental controls.

Papain was obtained from Boehringer Mannheim. The level of amidase activity in the papain suspension was measured periodically by the colourimetric assay of Arnon[18], involving the hydrolysis of *N*-benzoyl-D,L-arginine-*p*-nitroaniline into benzoyl arginine and the coloured compound *p*-nitroaniline. The absorbance of the *p*-nitroaniline product was measured at 410 nm. A unit (*U*) of papain activity is defined as that amount of enzyme activity that will liberate one mole of *p*-nitroaniline in one minute at 25°C at pH 7.5. The specific activity is expressed as the number of units of activity per microgram of protein. The specific activity of papain was found to decrease linearly with time at a rate of 6.4%/day. To provide relatively constant enzyme activity, treatment media were changed once every two days. In this way, the average specific activity of papain was 12.5 + 0.9 *U*/g. The two enzyme activities used in the experiments were 42 *U*/μl and 75 *U*/μl.

Papain activating agent solution-treated and distilled water-treated, and untreated samples were used as controls. The activating agent for papain was a freshly prepared solution of 0.05 M cysteine and 0.02 M EDTA in



Hard segment



Soft segment

Figure 1 Chemical structure of PEUU

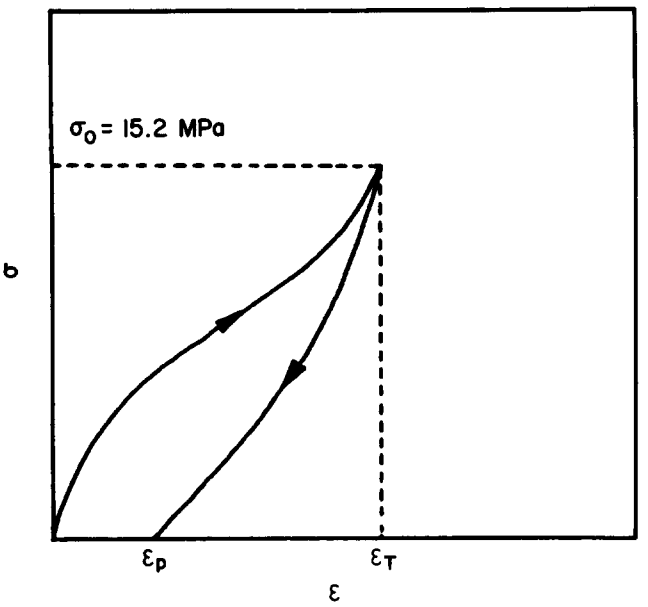


Figure 2 Schematic stress–elongation curve of the first cycle in the fatigue experiment

pH = 6.5 buffer solution. All control solutions were also changed once every 2 days. To inhibit bacterial growth, 0.02%w/v of sodium azide was added in all experimental solutions.

Films were immersed for 2 weeks or 1 month and maintained at 37°C. Sample containers were covered by aluninium foil during the treatment period. After treatment, samples were removed and cleaned by the procedure previously described[16], which basically involves repeated sonication in a solution of 1% v/v triton X-100, followed by 1% v/v liquid Ivory soap solution, and then repeated spraying with distilled water. The specimens were air dried for one day. Subsequently, the specimens were further dried in an oven at 60°C for 15 min. The dry samples were then wrapped in aluminium foil and stored in a desiccator prior to analysis.

Tensile and fatigue experiments

Mechanical properties were determined using a Model TTC Instron tensile machine. Untreated samples and samples treated for two weeks and one month were tested. The samples were cut out by a modelled blade cutter which provided a sample geometry with the narrowest part in the centre[16]. The geometry was designed so that samples would break at the centre.

Single loading experiments on the treated and untreated samples were carried out in air at room temperature. The strain rate was $10^3\%\,\text{min}^{-1}$. The treated and untreated samples were subjected to cyclic fatigue testing under a constant stress amplitude of 15.2 MPa in air at room temperature. *Figure 2* shows the fatigue process under constant stress conditions. The strain rate was $2 \times 10^3\%\,\text{min}^{-1}$ and the frequency was 2 to 3 cycles per minute. This experimental procedure causes a sample failure within 2 to 5 h. An average of 6 samples was obtained.

Optical microscopy

Treated and untreated samples were stretched from 0% elongation up to fracture by a mechanical stetcher, which was placed under an Olympus-BH-2 Transmission

Optical Microscope (OM). A polarizer filter was used to improve the contrast of image. Pictures were obtained at different sample elongations using an attached camera.

Statistical analysis

The variations in mechanical property data, as functions of treatment, were statistically analysed using the Student 't' test for unpaired samples. A 95% ($p < 0.05$) level of statistical confidence was utilized as the criterion for significance.

RESULTS AND DISCUSSION

Single loading experiments

The stress–elongation curve of the unstabilized PEUU was essentially unchanged by two weeks exposure to the aqueous control solutions. The curve for enzyme treated specimens was also indistinguishable from the controls except for a small but significant decrease in fracture stress (*Table 1*). The results of the single loading experiments for the unstabilized PEUU treated for one month are illustrated by the stress–elongation curves in *Figure 3*. In the low strain region there is no effect of treatment on the curve, and the calculated 100% secant modulus did not significantly change after treatment. Significantly lower fracture stresses were observed for all treated samples compared with the untreated control (*Table 1*). The fracture stress was reduced 20% by the distilled water or activating agent solution treatment, 25% by the papain (42 $U/\mu l$) treatment, and almost 50% by the papain treatment at the higher enzyme concentration (75 $U/\mu l$). The effect of papain was significant, even when the untreated PEUU was replaced by the water treated PEUU as the statistical control. Furthermore, *Figure 3* indicates that the elongation at break was concomitantly reduced by the treatment conditions. However, the magnitudes of the observed decreases, while consistent, were insufficient to establish statistical significance.

A marked change from the results obtained with the unstabilized PEUU was observed if stabilizers were incorporated into the PEUU. Two week and one month aqueous control treatments produced no change in the stress–elongation relationship. This is illustrated by the values for the fracture stress in *Table 1*. No significant decrease in fracture stress was observed after two week papain treatment of stabilized PEUU. For the one month test period, all the papain treated samples had significantly lower fracture stresses, although the effect was small compared with the results for the unstabilized PEUU. These observations are similar to those of Phua and coworkers[16] who used the commercial (stabilized) biomedical elastomer, Biomer®, and a lower papain concentration, but otherwise very similar test environments. Clearly the incorporation of either stabilizer combination in the polymer effectively eliminates the effects of the water and activating agent test environments, and reduces the enzyme-mediated effect on the fracture stress from 50% to approximately 20% of the untreated control.

Optical microscopy of unstabilized PEUU samples indicated that the enzyme environment promoted changes in the microdeformation behaviour. At large elongations, strain heterogeneity is observed at the micron size scale. An optical micrograph of the untreated PEUU strained to 900%, *Figure 4a*, shows numerous micronecks perpendicular to the direction of stress. The micronecks are fairly uniform in diameter and cover the entire specimen. At a higher strain just prior to fracture, *Figure 4b*, thin fibrils appear to span some of the micronecks suggesting that the material in the microneck subfibrillates as it is drawn thinner to produce craze-like structures. The deformation behaviour of a sample treated for one month with the higher enzyme concentration is shown in *Figure 5*. The micronecks which form at 900% strain have a striated appearance suggestive of a fibrillar structure. Moreover, there appear to be regions of high deformation, for example on the right side of the micrograph in *Figure 5a*, where fibril

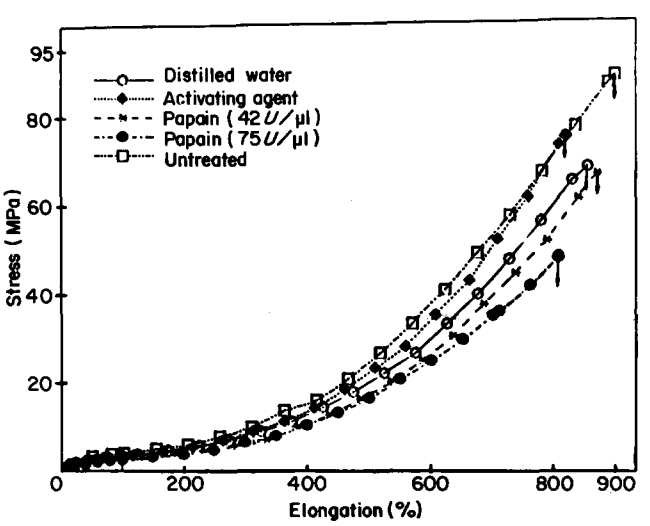


Figure 3 Stress–elongation curves of treated (1 month) and untreated, unstabilized PEUU samples

Table 1 Ultimate tensile stress of treated and untreated PEUUs

Treatment	Ultimate tensile stress (MPa)				
	Unstabilized PEUU		Stabilized (I) PEUU		Stabilized (II) PEUU
Medium/time (weeks)	(2w)	(4w)	(2w)	(4w)	(4w)
Untreated control	90.3	90.3	91.9	91.9	88.7
Water	90.5	72.3[a]	92.5	89.5	83.0
Activating agent solution	85.7	77.8[a]	91.4	81.0	86.1
Papain (42 $U/\mu l$)	–	70.0[a]	–	–	–
Papain (75 $U/\mu l$)	76.5[a]	51.0[a]	88.5	76.6[a]	71.4[a]

Mean values are shown ($n = 6$). The mean standard deviation of the results = 3.6 (MPa)
[a]Statistically significant at the 95% confidence level ($p < 0.05$) when compared with the mean control value

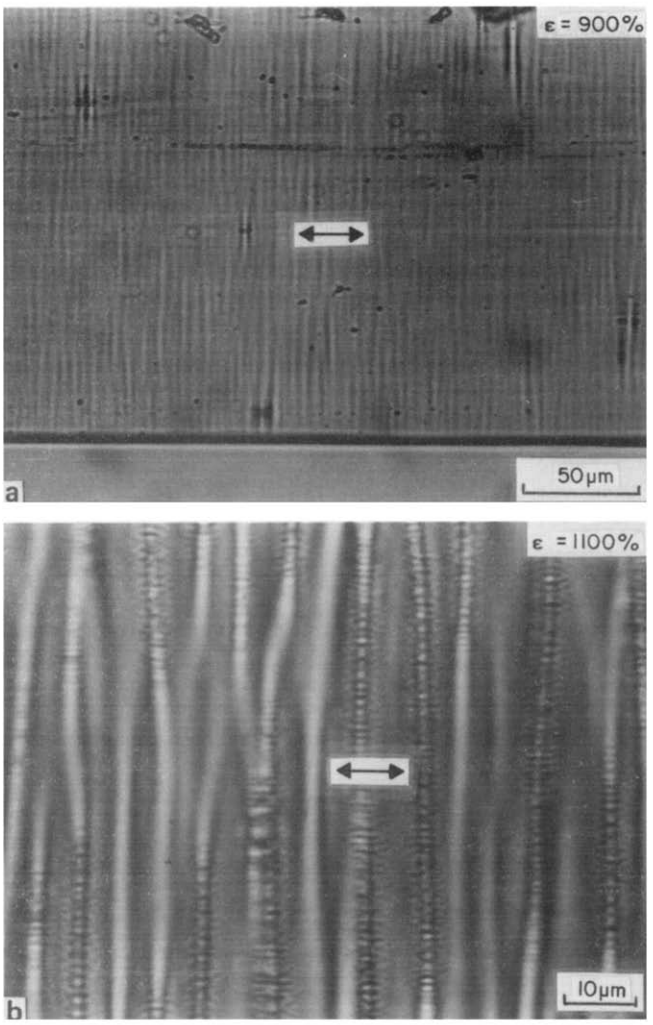


Figure 4 Optical micrographs of the untreated, unstabilized PEUU. (a) 900% elongation, (b) 1100% elongation

structure is clearly evident. At the higher strain, *Figure 5b*, the micronecks have been completely replaced by profuse fibrillation which is very similar in appearance to crazing. Very little is known about these craze-like structures in polyurethanes, although similar structures have also been observed in a polyester urethane at high elongation[19]. They have a striking resemblance, albeit on a different size scale, to the well-known crazes of glassy polymers such as polystyrene. Any analogies must be made with considerable care, nevertheless, it is well known that the effect of increasing molecular weight of polystyrene is to change the mode of microdeformation from microcracking to crazing with increasingly dense fibrillation to finally micronecking at very high molecular weight[20-22]. The propensity of micronecks in the enzyme-treated specimens to subfibrillate suggests that enzymatic degradation has the effect of decreasing the molecular weight. Subsequently, the strength of the microneck material in the lateral direction is reduced and voiding with fibril formation becomes more apparent.

Fatigue studies

The fatigue lifetimes of unstabilized PEUU samples are shown in *Figure 6*. All the samples failed by a parabolic crack front, which is a well known phenomenon for fatigue failure of elastomers. The cycles to failure for all one month treated samples were significantly lower than the untreated control. The cycles to failure were reduced 40% by the distilled water or activating agent solution, 53% by the papain solution (42 $U/\mu l$), and 67% by the papain solution of high activity (75 $U/\mu l$). The effect of the papain treatment was significantly greater than that for aqueous treatment alone. When the treatment period was

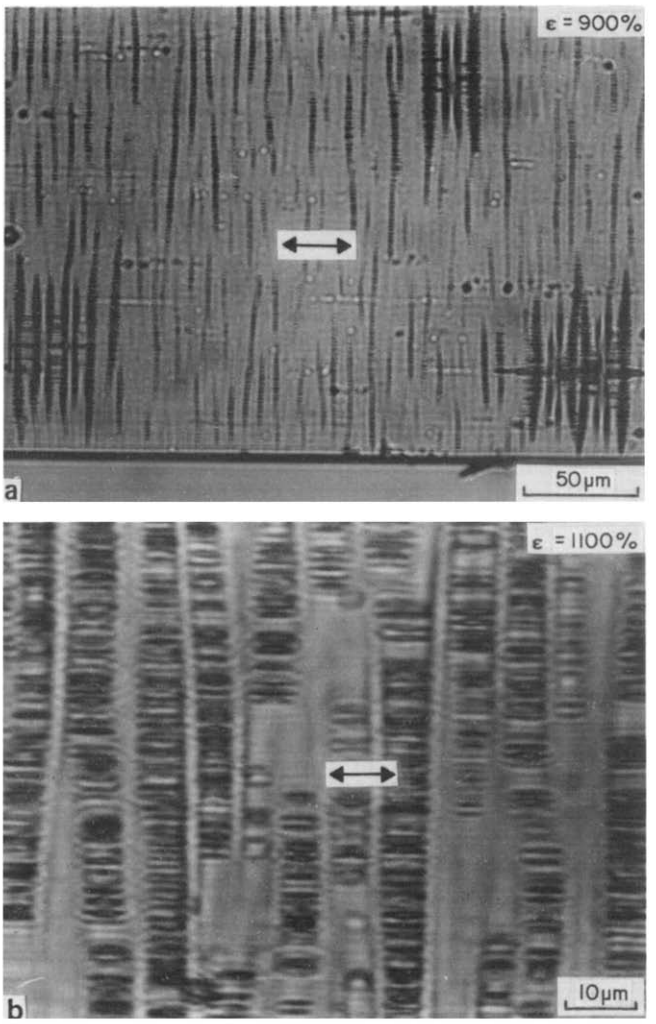


Figure 5 Optical micrographs of enzyme treated (1 month), unstabilized PEUU. (a) 900% elongation, (b) 1100% elongation

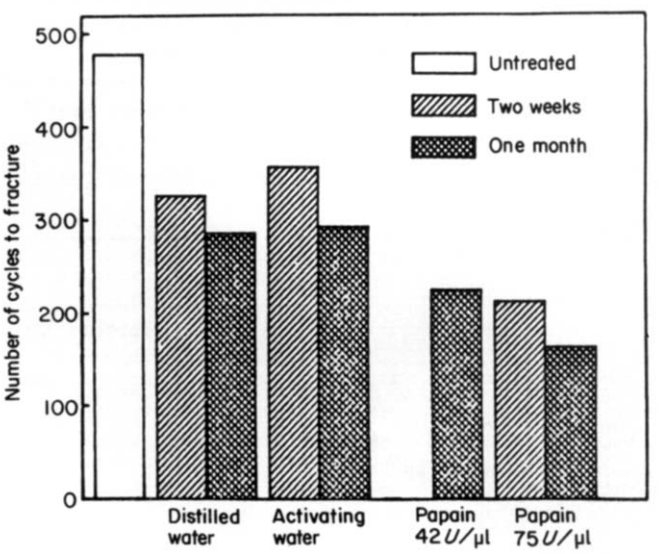


Figure 6 Fatigue lifetimes of treated and untreated, unstabilized PEUU

reduced from one month to two weeks, the fatigue lifetimes were longer by approximately 10%, but remained significantly lower than the untreated control.

The importance of including stabilizers in biomedical PEUU elastomers is emphasized by the results of the fatigue studies. The cycles to failure for stabilized and unstabilized PEUU's are compared in *Table 2*. For stabilized samples treated for 2 weeks, no significant variations from the untreated control value were observed. At one month, only papain treated samples demonstrated a significant decrease in fatigue lifetime and the decrease was not as large as that for the unstabilized PEUU. Other aqueous treatments had no significant effect on the fatigue lifetime of the stabilized samples after one month.

While the effects of environmental degradation of PEUU's have been observed in both the stress–elongation behaviour and the fatigue lifetime, the stress–elongation relationship appears to be the least sensitive method of mechanical analysis when compared with measurements of the ultimate failure properties. This is not surprising since initial degradation affects only the surface and hence may impact on crack initiation and failure processes without affecting bulk properties. Thus, a significant decrease in the fracture stress was observed following some treatments even though the stress–elongation relationship at lower elongations was not altered. The cycles to failure in fatigue was an even more sensitive indicator of environmental damage and, consistent with previous findings[16], a significant decrease in fatigue lifetime could reveal damage of the PEUU when the stress–elongation relationship was not altered.

Although the number of cycles to failure is an important parameter in fatigue measurements, other information can be obtained during the fatigue experiment which provides further insight into the fatigue process. The number of cycles to crack initiation and for crack propagation, given in *Table 3*, provides some insight into the differences in fatigue lifetime. During the fatigue test, the crack initiates from a microscopic edge crack or from a hole in the test specimen. The results in *Table 3* show that significant differences are seen with respect to the number of cycles to crack initiation, whereas the number of cycles for crack propagation does not vary significantly among all treated samples and the untreated control. Thus, lower fatigue lifetime corresponds to earlier onset of crack initiation.

The initiation of cracks is the culmination of accumulated damage at a flaw, and it follows that the treated PEUU's, weakened by the treatment, are more susceptible to damage during subsequent cycling. The constant stress condition chosen for the fatigue testing produced elongations in the range of 400–500% where significant differences between treated and untreated samples of the unstabilized PEUU are apparent in the stress–elongation curves. Thus the damage induced by the treatment is reflected as larger strains in cyclic fatigue loading and subsequently earlier failure. This effect for the unstabilized PEUU is seen in the total and permanent elongation on the first cycle, *Figure 7*. Treatment with the higher enzyme concentration results in a total elongation of about 490% on the first cycle compared with 415% for the untreated control, and a permanent elongation that is more than double. Damage induced by aqueous treatments without the enzyme is also apparent especially in the higher permanent elongation which indicates a loss of elasticity. Further damage accumulates as cycling proceeds and this results in a gradual increase in the elongation as the number of cycles increases. An almost logarithmic increase in both total elongation and permanent elongation is seen. From the slightly higher slope in *Figure 7*, it appears that damage accumulates more rapidly during cycling when the sample has been previously exposed to the enzyme.

The total and permanent elongations of a stabilized (I) PEUU, *Figure 8*, do not show any effects of treatment during the first 50 fatigue cycles. Although the enzyme-treated samples exhibited significantly shorter fatigue lifetimes as compared with the controls, neither damage caused by the enzyme during treatment, nor enhancement of damage accumulation during cycling, is apparent in the early part of the fatigue experiment.

Chemical analysis of the unstabilized PEUU has suggested that the aqueous treatments promote degradation of the polyether soft segment regions[17]. These regions play an important role in the mechanical properties of polyurethanes. They act as springs between

Table 3 Number of cycles for crack initiation and propagation in unstabilized PEUU

Treatment medium	Crack initiation (cycles)	Crack propagation (cycles)
Untreated control	472±84	27±17
Water	270[a]±40	24±15
Activating agent solution	266[a]±32	35±11
Papain (42 *U*/μl)	189[a]±24	34±10
Papain (75 *U*/μl)	135[a]±32	22±8

Treatment time = 1 month
Mean values ± standard deviation are shown ($n=3$)
[a]Statistically significant at the 95% confidence level ($p<0.05$) when compared with the mean control value

Table 2 Fatigue lifetime of treated and untreated PEUUs

Treatment	Cycles to failure				
	Unstabilized PEUU		Stabilized (I) PEUU		Stabilized (II) PEUU
Medium/time (weeks)	(2w)	(4w)	(2w)	(4w)	(4w)
Untreated control	478	478	475	475	325
Water	327[a]	287[a]	470	448	338
Activating agent solution	358[a]	294[a]	492	341	301
Papain (42 *U*/μl)	–	226[a]	–	–	–
Papain (75 *U*/μl)	214[a]	165[a]	452	264[a]	190[a]

Mean values are shown ($n=6$). The mean standard deviation of the results = 88.6 cycles
[a]Statistically significant at the 95% confidence level ($p<0.05$) when compared with the mean control value

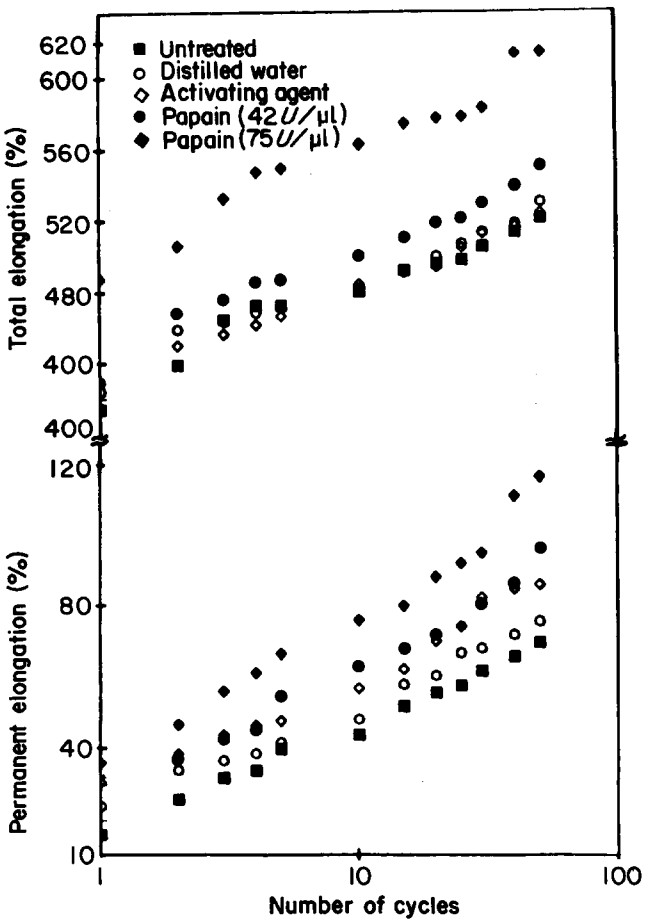


Figure 7 Permanent and total elongation of treated (1 month) and untreated, unstabilized PEUU for the first fifty fatigue cycles

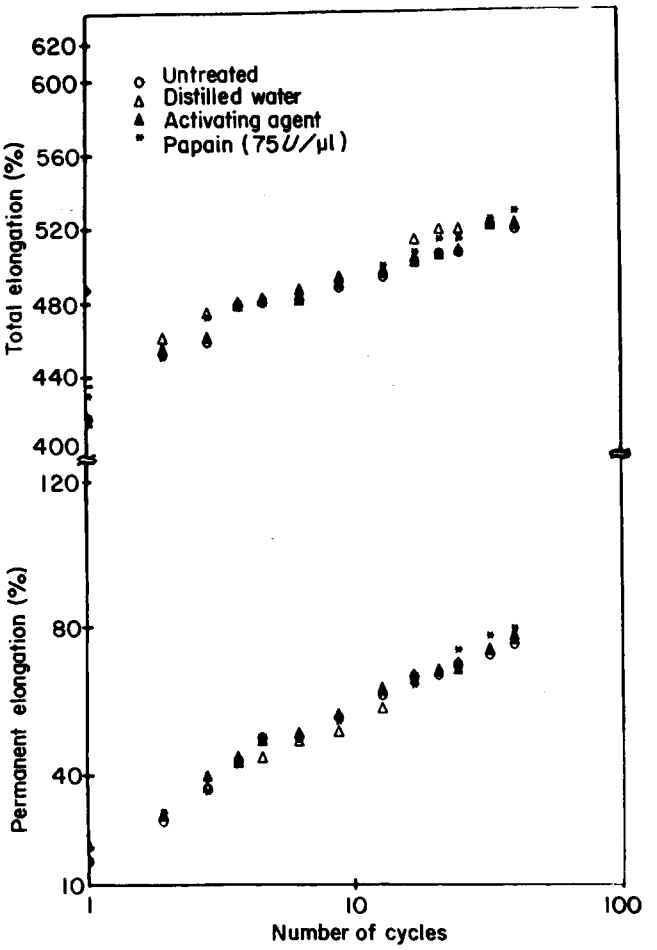


Figure 8 Permanent and total elongation of treated (1 month) and untreated, stabilized (I) PEUU for the first fifty fatigue cycles

hard segment regions to provide the large elongations and rapid recovery which are characteristic of these materials. It is thought that stress crystallization in the soft segment regions at high elongation is responsible for the unusual fracture toughness of polyurethane elastomers[19,23]. Consequently, the observed loss in mechanical strength and elasticity is consistent with a degradation process which damages the soft segment regions. The addition of stabilizers such as radical chain terminators or u.v. absorbers was found to inhibit degradation and loss in mechanical performance under aqueous conditions. This is consistent with the belief that chemical degradation of the polyether soft segment involves a free radical oxidative mechanism[24,25]. From the medical perspective, it is highly desirable for implanted polymers to be additive-free. However, if the mechanical performance of PEUU's is to be maintained for extended periods, the need for added stabilizers appears unavoidable.

The deterioration of mechanical properties was accelerated by exposure to enzyme. For the unstabilized PEUU, the degradative effect of the enzyme was superimposed on that of the aqueous environment and depended on the enzyme concentration. Stabilizers which were effective against the aqueous environment did not inhibit enzymatic degradation. It has been suggested that enzymatic degradation may occur by a different mechanism involving specifically cleavage of urethane or urea linkages[17]. While the highest concentrations of these groups are in the hard segment regions, the crystalline nature of the hard segment regions renders them less susceptible to chemical attack than the soft segment regions, and subsequently the most accessible urea and urethane linkages are those located in the interphase between hard and soft segments regions. Subsequently, loss of connections between phases by chain cleavage reduces the mechanical coupling between hard and soft segment regions and produces results similar to aqueous degradation of unstabilized PEUU, specifically loss of strength and elasticity. The effects of damage to the network structure are clearly seen when the material was strained to high elongations in the optical microscope. Formation of holes separated by fibrillar structures, when prior to degradation a continuous microneck was seen, is characteristic of decreased molecular weight and loss of network continuity, and is attributed to the increase in unrestrained chain ends which create sites of weakness for void formation. Coalescence of voids as the fibrous material between them fails eventually leads to microcracks and premature failure.

CONCLUSIONS

Deterioration in the mechanical properties has been observed when a PEUU elastomer is exposed to the proteolytic enzyme papain. Specifically, it has been found that:

(1) Degradation of unstabilized PEUU is observed in aqueous environments, the effect of enzyme is superimposed on that of the aqueous media alone.

(2) Free radical and u.v. stabilizers inhibit the effect of

the aqueous environment but are not effective against the enzyme.

(3) Degradation of PEUU initially affects the fracture properties, particularly the fatigue lifetime; as degradation proceeds the bulk properties as revealed by the stress–elongation relationship also deteriorate.

(4) A change in the microdeformation behaviour from micronecking to crazing is indicative of decreased molecular weight and results in premature fracture.

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