

***In vitro* degradation of poly(ester-urethanes) for biomedical applications**

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Degradation studies on a series of polyesterurethanes having different compositions of hard and soft blocks have been performed utilizing an accelerated test method. Degradation was followed by titrimetry, mass loss, mechanical properties and infrared spectroscopy. As the number of methylene groups present within the polyester moiety was increased, the resistance to degradation also increased. The presence of an aromatic component in the hard block reduced the rate of hydrolysis but the degradation in mechanical properties was accelerated.

1. Introduction

The subject of polymer degradation is of considerable importance in medical engineering and pharmaceutical technology. There are many situations in which ostensibly inert polymers are used for the construction of prostheses and implanted in the tissues of the body where it is intended they remain for a considerable period of time. It frequently happens, however, that these polymers are in practice slightly degraded by the physiological environment [1]. An understanding of this phenomenon is of paramount importance since the biocompatibility of the implant may be compromised. The study of such degradation is not necessarily straightforward since changes of great consequence may be very subtle from the structural point of view. In biomedical applications, environmental stability tends to be particularly important in three areas; processing, sterilization, and long-term implantation. Degradation during processing is primarily thermal in nature, sterilization effects can be thermal, radiative, or hydrolytic, depending upon the sterilization technique used. In the physiological environment, the only feasible degradation mechanisms are hydrolysis and oxidation. For hydrolysis to occur the polymer must contain hydrolytically unstable bonds and show some degree of hydrophilicity. For hydrolysis to occur *in vivo* a further constraint is applied, that the reaction should proceed at a pH of around 7.4 and a temperature of 37 °C. *In vivo* degradation of polymers is also complicated by the possible involvement of agents such as enzymes, an effect detected *in vitro* by Smith *et al.* [2-4].

This paper reports on a study of the *in vitro* degradative behaviour of a number of degradable polyesterurethanes synthesized in our laboratories for use as non-adhesive films for the prevention of adhesions after surgery. Considering the wide applications and extensive use of polyurethanes in biomedical and non-biomedical systems, it is surprising that our present understanding of the degradation of polyurethanes is incomplete. Most commercial polyurethanes (espe-

cially polyetherurethanes) are regarded as possessing excellent resistance to aqueous environments; however, the presence of ester or ether linkages in the backbone of a polymer inevitably results in some degree of hydrolysis. It is the rate of hydrolytic degradation of these materials that is of prime importance; this varies over a wide range and is dependent on the chemical structure of the particular polyurethane. The hydrolytic stability of polyester and polyether urethanes has been extensively investigated by Schollenberger [5], who found that hydrolytic degradation can be ranked in the following way:



For polyesterurethanes, there are two possible hydrolysis mechanisms, the most probable involving cleavage of the ester link producing two shorter chains (Fig. 1a). The other possibility is cleavage of the urethane linkage. This case is only favoured if a polyesterurethane contains sterically hindered carboxyl ester linkages [5] (Fig. 1b).

In this study, polyesterurethanes of varying nature and ratios of hard and soft segments based on adipate type esters having about the same molecular weights were subjected to an accelerated hydrolysis regime. Degradation was followed by a number of analytical techniques in an attempt to identify those that could be adopted for a standardized procedure.

2. Materials and methods

Poly(ester-urethanes) synthesized in our laboratory were used in this study. The synthesis procedure is described elsewhere [6].

Thin films were cast from a 6% solution of polymer in THF. To obtain uniform thickness, casting was carried out on a smooth surface pre-levelled using a spirit level. Films were dried under vacuum at room temperature over silica gel and punched out into dumbbell tensile test specimens using a precision

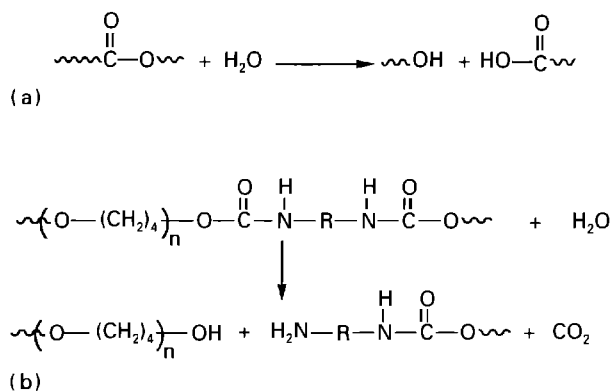


Figure 1 Hydrolysis mechanisms for polyesterurethanes.

manual punch. The dumbbell specimens had the following dimensions: gauge length = 3.5 cm, width = 3 mm. The specimens were cut cleanly with no nicks or imperfections in the edges. Polymer samples were subjected to an accelerated degradation test involving the total immersion of the test samples as follows:

Film samples were accurately weighed (approximately 0.1–0.3 g of polymer) and placed in a 250 ml conical flask. Carbon dioxide-free water was used to make 1 M NaOH. 50 ml of this were then added to the conical flask which was subsequently stoppered. The flask was placed in an incubator, maintained at $37^\circ\text{C} \pm 1^\circ\text{C}$ for periods of one, two, three and four weeks. Samples were exposed in triplicate. After the desired reaction time, the flasks were removed and the unreacted NaOH was determined by titrating with 1 M HCL, being a modification of the method proposed by Davies [7].

After titration, the films were washed and rinsed in distilled water several times and placed between clean sheets of porous filter paper to remove moisture. The films were then stored in a desiccator (in the dark) under vacuum for a period of one week.

A blank, omitting the sample, was run and the difference used to calculate the amount of hydrolysis. A value for the theoretical amount of hydrolysis was obtained as follows:

0.2–0.3 g of polymer film was accurately weighed and placed in a 250 ml flask equipped with a water condenser. 50 ml of 1 M NaOH was added and the contents boiled for 12 h, cooled to room temperature and the unreacted alkali determined by titrating with 1 M HCL. A blank, omitting polymer, was also run and the difference used to calculate the theoretical hydrolysis.

The degree of hydrolysis of the polymer samples was calculated as mg of NaOH/g of polymer and expressed as a percentage of the theoretical hydrolysis possible.

Degradation was monitored using Fourier transform infrared spectroscopy (FTIR), tensile testing and mass analysis.

FTIR analysis was carried out using a NICOLET 730 FTIR instrument, purged with compressed, filtered and carbon dioxide-free air. All spectra were obtained using an attenuated total internal reflection (ATR) technique. A KRS-5 crystal (obtained from SPECAC) with an angle of 45° was used to obtain

spectra of the film samples. Spectra were obtained by averaging 128 scans at 4 cm^{-1} resolution.

Mechanical analysis of the degraded films was carried out using a J.J. Instruments table-top testing machine with a 50 N load cell. All testing was carried out at room temperature (20°C) at a strain rate of 100 mm/min. The thickness of each specimen, over the gauge length, was measured prior to testing by using a micrometer dial gauge mounted on a solid smooth aluminium block. Four measurements of thickness were taken along the gauge length of each specimen and the average value recorded. The initial Young's modulus of the specimens was calculated from a tangent to the Hookean region of the curves obtained. Yield stress values were also recorded for all specimens tested.

3. Results and discussion

The type of polyester incorporated into a polyurethane has a controlling influence on the rate of hydrolysis. Structures of ester oligomers used in the synthesis of polyurethanes are given in Fig. 2. Polyesters having about the same molecular weights were utilized in this study and the results indicate that decreasing the methylene (CH_2) group content of the polyester, increases the rate of hydrolysis. This is most easily seen in the titration results and the mass loss data given in Figs 3 and 4, respectively.

Tensile testing provided an excellent source of measuring the rate of hydrolysis and the results obtained were similar to those obtained from percentage mass loss and titration methods. Films of polyurethanes based on PEAG were completely broken down into fragments after one week making tensile testing impossible, whereas polyurethane films based on poly(tetra- and hexamethylene adipate) glycols and polycaprolactone diol held their strength sufficiently to perform tensile testing.

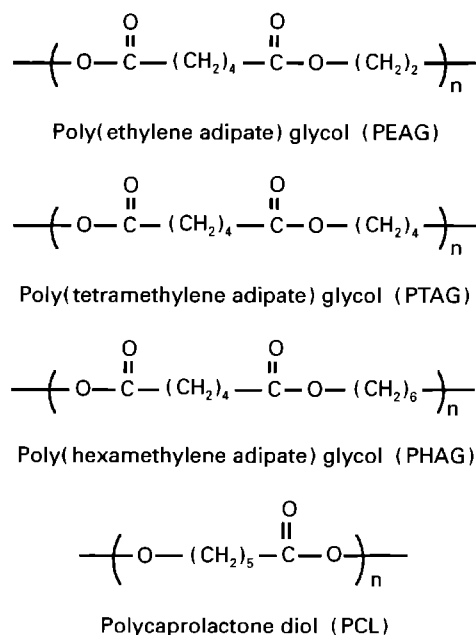


Figure 2 Structures of ester moieties used in polyesterurethane synthesis.

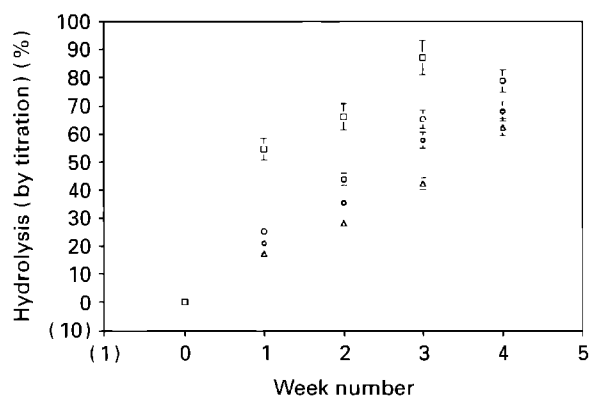


Figure 3 Hydrolysis measured by titration for MDI-based polyesterurethanes: □ AR/PEAG; ◇ AR/PHAG; ○ AR/PTAG; △ AR/PCL.

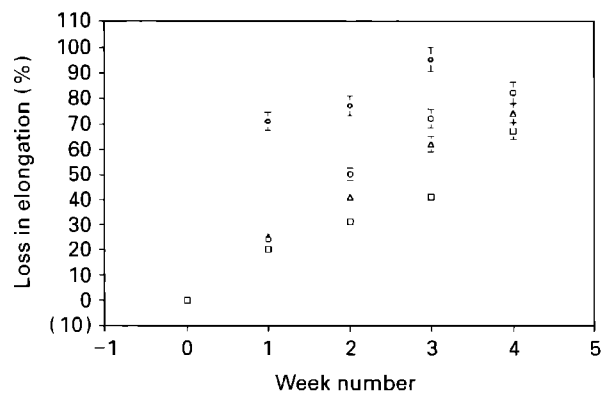


Figure 5 Hydrolysis measured by loss in elongation for MDI-based polyesterurethanes: □ AR/PCL; ◇ AR/PEAG; ○ AR/PTAG; △ AR/PHAG.

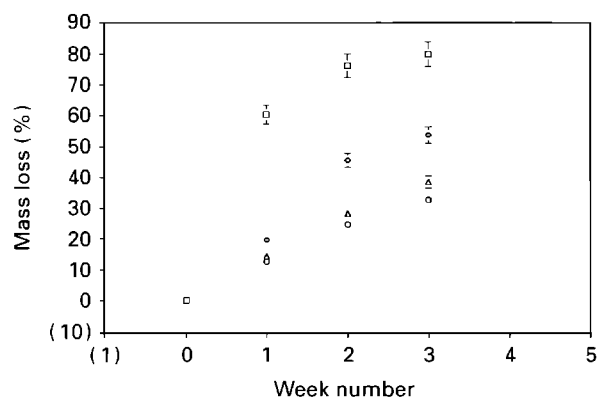


Figure 4 Hydrolysis measured by mass loss for MDI-based polyesterurethanes: □ AR/PEAG; ◇ AR/PTAG; ○ AR/PHAG; △ AR/PCL.

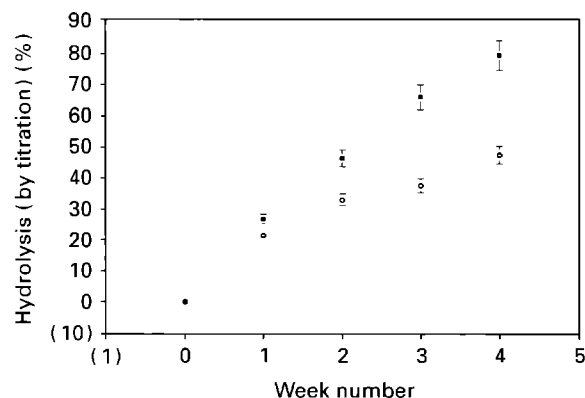


Figure 6 Hydrolysis measured by titration for MDI and H₁₂MDI based polyesterurethanes: ■ AL/PTAG; ◇ AR/PTAG.

Loss in percentage extensibility brought about by hydrolysis provides a good measure of the rate of degradation, confirming that the number of methylene groups present in the polyester moiety greatly affects the hydrolysis rate of polyurethanes (Fig. 5).

The results obtained in this study are comparable with those reported by Schollenberger [5] who suggested that polyurethanes based on esters having larger numbers of methylene groups had better hydrolytic stability. Fig. 5 shows that polyurethanes based on polyethylene adipate glycol underwent a rapid loss in percentage elongation whereas those based on hexamethylene adipate glycols saw a more gradual decrease.

The nature of the diisocyanate used in manufacturing polyurethanes also influences the hydrolysis rate. The effect of MDI and H₁₂MDI on the rate of hydrolysis is shown in Figs 6, 7 and 8. Polyurethanes based on MDI hydrolyse more slowly than those based on H₁₂MDI (Fig. 6). However, the effects of this hydrolysis on the mechanical properties is more severe in the case of MDI than for H₁₂MDI (Figs 7 and 8). The increase in 4% modulus values observed at 1 week immersion (Fig. 7) was a reproducible effect. A number of researchers have reported similar experimental evidence for the effects of hard block composition [8, 9].

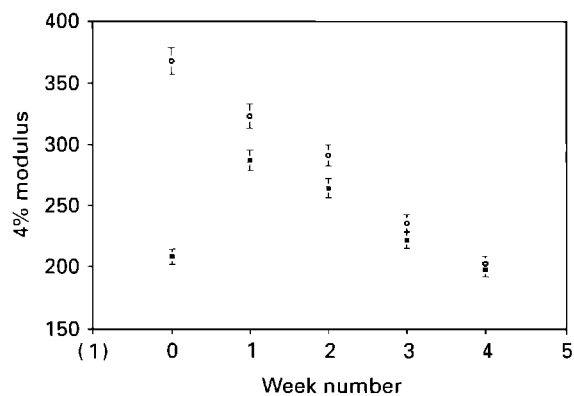


Figure 7 Hydrolysis measured by change in 4% modulus for MDI and H₁₂MDI based polyesterurethanes: ■ AL/PTAG; ◇ AR/PTAG.

Hydrolytic degradation changes the chemical composition of polyurethanes which manifests itself in an increase in hydroxyl and carboxylic groups. These changes are readily seen in the infrared spectra of degraded specimens, the broadening of the peak centred at 3332 cm⁻¹ indicates the formation of hydroxyl groups (Fig. 9). This broadening effect was observed in all spectra of hydrolysed samples.

Polyesterurethanes degrade via breaking of ester linkages and result in a loss of ester-carbonyl groups.

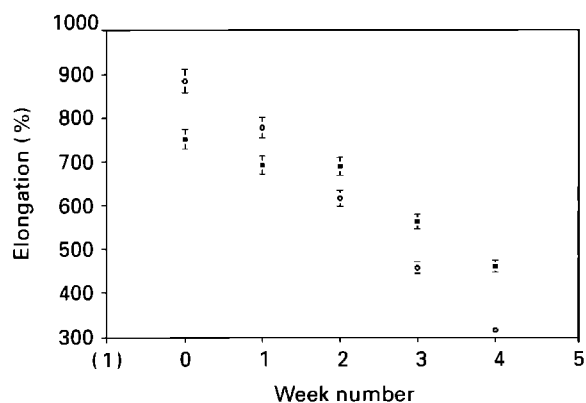


Figure 8 Hydrolysis measured by percentage elongation for MDI and H₁₂MDI based polyesterurethanes: ■ AL/PTAG; ◇ AR/PTAG.

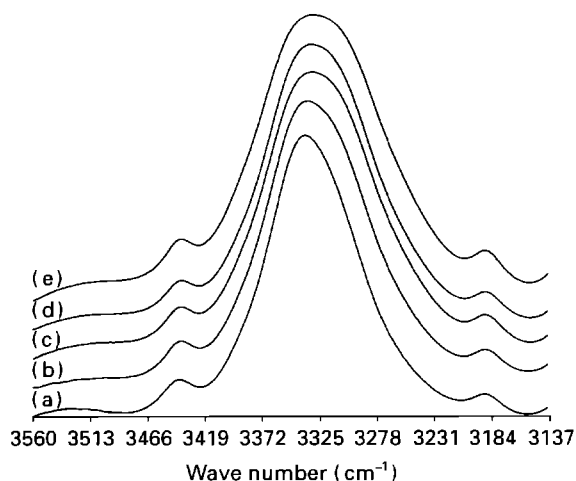


Figure 9 Hydroxyl region of the infrared spectrum of degraded polyesterurethanes: (a) original material; (b) after 1 week immersion; (c) after 2 weeks immersion; (d) after 3 weeks immersion; (e) after 4 weeks immersion.

This was evident from a decrease in the peak area centred at 1736 cm^{-1} which corresponds to the ester carbonyl. Initially a narrowing and decrease in the

area of the peak was observed suggesting a loss of ester carbonyl, followed by peak broadening, possibly confirming carboxylic group formation. Breakage of the ester linkages was also confirmed from a decrease in the areas of peaks centred at 1280 and 1180 cm^{-1} . Loss in peak area at this region confirmed that polyesterurethanes did hydrolyse via ester linkage producing two smaller chains giving rise to two more carboxylic and hydroxyl groups.

4. Conclusions

This study has shown the effect that the nature of both the hard and soft segment of a polyesterurethane has on degradative behaviour. As the number of methylene groups present within the polyester moiety increases, the resistance to degradation also increases. The presence of an aromatic component in the hard block reduces the rate of hydrolysis but the degradation of mechanical properties is accelerated.

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