Biodegradable polymers for use in surgery—poly(ethylene oxide) poly(ethylene terephthalate) (PEO/PET) copolymers: 1

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The requirement for a biodegradable material in surgery is discussed. The synthesis of a series of biodegradable polymers based on the copolymers of polyethylene oxide (PEO) and polyethylene terephthalate (PET) are described. The synthesis of copolymers in the range 50—70 wt % PEO was followed by time sampling techniques with subsequent characterization of the samples being undertaken by gel permeation chromatography (g.p.c.), ^{13}C nuclear magnetic resonance spectroscopy (n.m.r.) and infra-red spectroscopy (i.r.). Details of the g.p.c., n.m.r. and i.r. analysis are described. The morphology of the copolymers as a function of composition was studied by differential scanning calorimetry (d.s.c.) and X-ray crystallography. Tensile properties as a function of composition are reported and compared with current materials used in surgery.

INTRODUCTION

Copolymers of polyethylene oxide (PEO) and polyethylene terephthalate (PET) were first described by Coleman[1,2] in 1954. This family of copolymers was studied in an attempt simultaneously to reduce the crystallinity of PET and increase the hydrophilicity to improve dyeability with hydrophilic dyes.

PEO/PET copolymers have been mentioned occasionally in the literature since, however, in each case the specific combination of segments has been used to reduce the crystallinity of the standard PET matrix and increase its hydrophilicity. Kenney[3] described the thermal and mechanical properties of one composition, and the effect of PEO content on moisture regain. Lyman et al.[4,5] used PEO/PET copolymers as haemodialysis membranes. The PET was chosen for its mechanical properties which allowed the fabrication of thin high tenacity membranes[4]; PEO was introduced as the cosegment to increase the permeability of the membrane to hydrophilic molecules. Annis et al.[6] used PEO/PET copolymers with increasing PEO contents to produce a series of surfaces of increasing energy in an attempt to produce zero interfacial energy between an implant and the adjacent biological connective tissue in sheep. Annis[6] found that the collagenous capsule formed around the implant approached the implant surface ever more closely as the PEO content increased. However, it was observed that the implants were unstable and fragmented over an 8 week period in subcutaneous tissue[6].

It was this casual observation i.e. that the implants degraded in the physiological environment, that prompted this study of the PEO/PET family of copolymers as possible candidates for 'biodegradable elastomers' which might have some practical use in medicine and surgery[7]. This paper describes the synthesis, characterization of structure, and the properties of part of this family of materials, Part II will describe the degradation mechanism and change in properties of these materials, when placed in the physiological environment[8].

The need

A 'biodegradable elastomer' has two major applications in surgery: firstly, as a temporary scaffolding i.e. a reinforcement until a wound has healed, or as a component of, for example, an artificial artery, that can be replaced by natural tissue in time; secondly, as a temporary barrier to prevent adhesion between natural tissue planes that have been damaged either by accident e.g. tendons, or as a result of surgery e.g. between the pericardium and the heart wall during open heart surgery.

The requirement

A material, (or family of materials) is required that has a controlled degradation with a predictable rate, (or range of rates), of loss of mechanical properties and mass. The products of degradation should be non-toxic, i.e. have no adverse effects on the surrounding tissues or systemic effects, and should be excreted from the body preferably by the kidney or lung in less than 6 months. Providing total excretion is accomplished within 6 months, experience has shown that long term carcinogenesis is unlikely if acute and subacute tests show the material to be non-toxic. Under these conditions, long term animal testing is not required by the FDA.

PEO/PET COPOLYMER STRUCTURE

The structure of a PEO/PET copolymer is shown in *Figure 1*: (x), the length of the PEO segment, can theoretically be varied at will but the commercially available polyethylene glycols (PEG) are listed in *Table 1*.

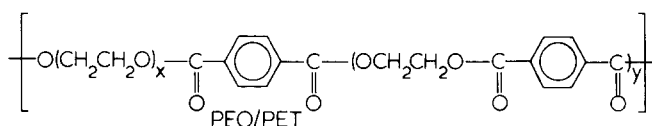*Table 1* shows that the average number of ethylene terephthalate (ET) units (y) in the PET segment varies not

Figure 1   Structure of PEO/PET copolymers

Table 1   Theoretical segments lengths of PEO/PET copolymers

$\bar{M}_n$ PEG	Average no. E. O. units in PEO segment	Average no. E. T. units in PET segments wt. % PEO		
		50	60	70
200	5	1	1*	1*
400	10	2	1–2	1
600	15	3	2	1–2
1000	25	5	3–4	2–3
1500	37	8	5	3
4000	100	20	14	9
6000	150	30	21	13

* Contains free PEG

only with PEO segment length, but also with mole (or weight) fraction.

In this study, weight fractions of PEO of 50–70% were chosen as being optimum. This range of compositions was known[6] to deteriorate under physiological conditions. These materials are soluble in common organic solvents, e.g. chloroform, and therefore characterization and fabrication is not difficult. Above 70 wt% PEO the materials have poor mechanical properties. Below 50 wt% PEO solubility is a problem. Polyethylene glycols of 600 and 1500 number average molecular weights were chosen to ensure that the longest PET segment would be approximately 8 units long.

SYNTHESIS OF PEO/PET COPOLYMERS

PEO/PET copolymers were synthesized by transesterification from di(2-hydroxyethyl) terephthalate (DET) monomer and either PEG 600 or 1540 (BDH) using antimony trioxide (Sb_2O_3) catalyst (BDH) and phosphoric acid (BDH) to complex trace quantities of transition metals present in DET which might cause depolymerization. The polyesterification was carried out on the 2 kg scale using a vacuum autoclave shown schematically in *Figure 2*.

A typical 60:40 PEO/PET composition was synthesized as follows[7]. 1100 gms of PEG (1540), and 918 gms of DET monomer were placed in the prereaction vessel and heated with stirring under dry N_2 until melting and homogenization was complete. 0.42 gms of Sb_2O_3, 0.70 gms H_3PO_4 were added, and the mixture was introduced into the autoclave at 200°C. The autoclave was flushed with dry nitrogen, the temperature was raised to 230°C and a vacuum of ~7 mmHg applied with subsequent elimination of ethylene glycol. The temperature was raised to 290°C over a 30 min period with continuous elimination of ethylene glycol. At 290°C, the vacuum was increased to ~0.5 mmHg and the polycondensation continued isothermally for 2 h.

The course of the polymerization was followed by a series of time sampling experiments. The observations and conclusions may be summarized as follows. No reaction occurs during melting in the absence of catalyst. Ethylene glycol is eliminated rapidly as soon as vacuum is applied, and the major reaction that takes place during the temperature rise from

230°–290°C is the formation of PET polymer with minimal incorporation of PEO. The resultant mixture is partially chloroform soluble and shows mainly unreacted PEO. Slow elimination of ethylene glycol continues with the application of full vacuum for the first hour and a mixture of PET, PEO and PEO/PET is present after this period. Elimination of ethylene glycol is limited during the second hour during which time transesterification takes place with the incorporation of PEO segments. A homogeneous, reproducible segmented copolymer is produced after 2 h reaction at 290°C and full vacuum. No improvement in homogeneity is observed by extending the period of reaction, in fact MW tends to fall between 2 and 3 h.

Homogeneity was determined by splitting the molecular weight distribution (MWD) into three parts using g.p.c.

This was accomplished by dividing the MWD seen by g.p.c. into three separate portions. Portion one covered the 'high' molecular weight end of the distribution while the second portion covered the 'medium' molecular weight band. Portion three consisted of the 'low' molecular weight area. By monitoring the elution volumes of these bands on the g.p.c. fractions of polymer were collected which corresponded to these three portions of the distribution. The compositions of each of these three fractions were determined by n.m.r. and i.r. spectroscopy. No differences in composition as a fraction of molecular weight were found.

Low vacuums due to leaks resulted in two problems, firstly the polymer was coloured due to oxidation of the polyether segment, and secondly the ultimate MW was lowered. At the end of the isothermal reaction, the vacuum was broken with
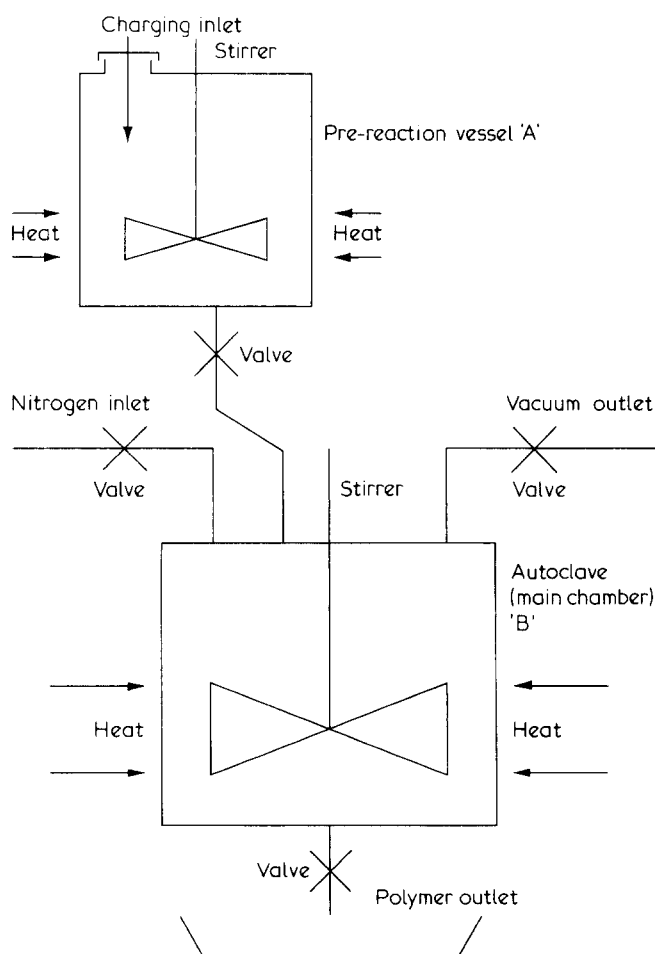

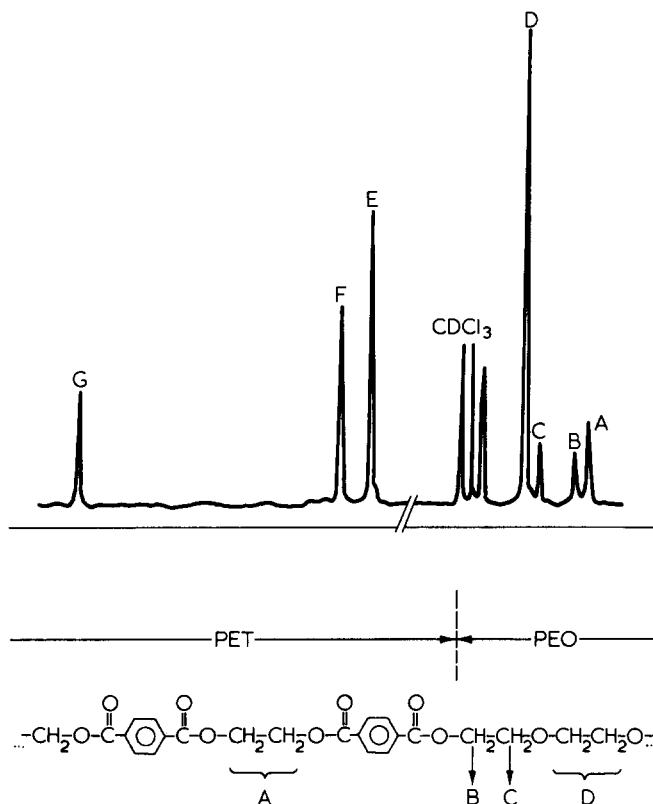*Figure 2*   Schematic diagram of polycondensation autoclave

Figure 3 ^{13}C n.m.r. spectrum of PEO/PET copolymer dissolved in CDCl$_3$

Assignments

A = 63.1 ppm   E = 129.9 ppm (aromatic carbons)
B = 64.6 ppm   F = 133.9 ppm (aromatic carbons)
C = 69.2 ppm   G = 165.7 ppm (carbonyl carbons)
D = 70.7 ppm

dry N_2 and the molten polymer run out of the autoclave into aluminium trays and allowed to solidify into ½" thick slabs.

The slabs were cut into ½" cubes on a bandsaw, dissolved in chloroform (Analytical Reagent Grade), filtered through a no. 1 Whatman filter and cast into 500 μ thick films on deactivated glass plates.

CHARACTERIZATION OF PEO/PET FILMS

Composition of PEO/PET copolymers were obtained using a ^{13}C Jeol SX100 spectrometer. A typical n.m.r. spectrum for a 50:50 PEO/PET composition, together with the peak assignments is shown in *Figure 3*. The composition can be obtained from the following expressions:

$$\text{Mol \% PEO} = \left[\frac{C + D}{A + B + C + D} \right] \times 100 \tag{1}$$

$$\text{Mol \% PET} = \left[\frac{A + B}{A + B + C + D} \right] \times 100 \tag{2}$$

The average number of EO units/PEO segment may be obtained, since if n = no. of EO units/segment, and x = units of integration/nucleus, then:

$$D = 2x(n - 1) \tag{3}$$

$$C = 2x \tag{4}$$

and by combining (3) and (4),

$$n = \frac{D}{C} + 1 \tag{5}$$

Similarly for the PET segment, m = no. of PET units/segment, and

$$A = 2x(m - 1) \tag{6}$$

$$B = 2x \tag{7}$$

and by combining (6) and (7)

$$m = \frac{A}{B} + 1 \tag{8}$$

Hence the average molar compositions can be obtained from equations (1) and (2), and the average lengths of the PEO and PET segments are obtained from equations (5) and (8) respectively.

The compositional data obtained from n.m.r. in CDCl$_3$ are shown in *Table 2*.

The results in *Table 2* show that the average compositions obtained experimentally are very similar to the theoretical values. However, in every case the PEO, and therefore the PET segment lengths measured experimentally are shorter than the calculated values. The reduction is greater than can be accounted for by instrument errors, i.e. 32 ± 2 for PEO segment length. *Table 2* suggests that the reduction in PEO segment length increases with PEO content.

The composition of PEO/PET copolymers can also be obtained from the ratio of infra-red absorbances at 730 and 2880 wave numbers. The calibration of this technique against composition obtained by n.m.r. is shown in *Figure 4*.

A further set of syntheses was undertaken, identical to those previously described except that DET monomer was omitted from the mixture in order that the effect of catalyst, acid, temperature and vacuum on the PEO segment would be identified. N.m.r. and g.p.c. showed the PEG 1500 to be degraded from $\bar{M}_n$ = 1300 initially to $\bar{M}_n$ = 1100 after the full polymerization sequence. No change in structure was seen during the preheating step. No change was found in the PEG 600.

The results show that the fall in PEO segment length from 32 to between 19 and 25 EO units observed during copolymerization is only partially explained by transesterification which reduces the PEO segment to 26 units. G.p.c. shows no significant changes in the MWD of the PEG after reaction.

Table 2 Typical compositions of PEO/PET copolymers from ^{13}C n.m.r.

wt % Composition theoretical	$\bar{M}_n$* PEO	wt % Composition experimental	PEO theo.	PEO expt.	PET theo.	PET expt.
50/50	1270	48/52	32	25.3	7–8	4.8
60/40	1270	57/43	32	22.1	5	3.8
70/30	1270	66/34	32	19.3	3	2.3
50/50	600	42/58	14	9.2	3.1	3.0
70/30	600	67/33	14	12.8	1.3	1.5

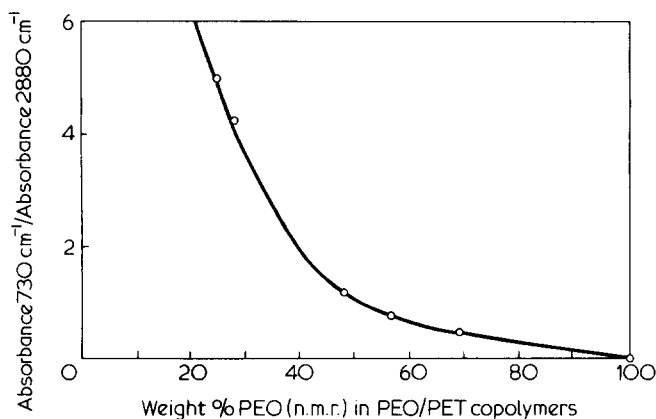* PEG 1540 as supplied had $\bar{M}_n$ = 1270, $\bar{x}_n$ = 32

Figure 4 Infra-red/composition calibration curve for PEO/PET copolymers

Table 3 Molecular weight parameters for PEO/PET copolymers

wt % composition	MW PEO	$\bar{M}_n \times 10^{-3}$	$\bar{M}_n \times 10^{-3}$	$\bar{M}_w/\bar{M}_n$
48/52	1100	12	48	4.1
57/43	968	11	69	6.1
66/34	836	17	64	3.7
42/58	600	11	102	9.3
67/33	600	0.4	3.2	8.0

A = Glass transition temperature   D = PET crystallisation
B = PEO crystallisation   E = PET melting point
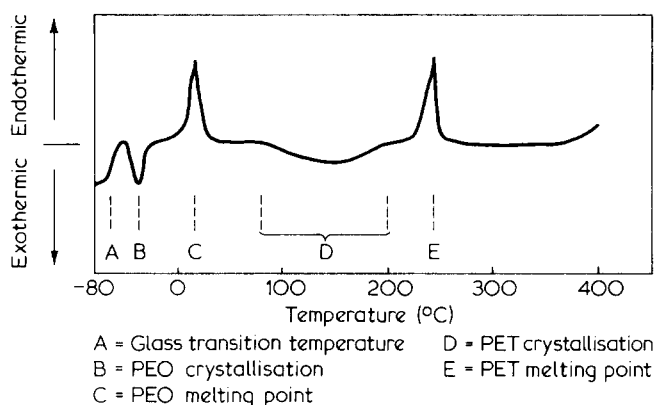C = PEO melting point

Figure 5 A typical d.s.c. thermogram for a 50/50 wt % PEO/PET copolymer. A, glass transition temperature; B, PEO crystallization; C, PEO melting point; D, PET crystallization; E, PET melting point

Further reduction in the PEO segment length occurs during the transesterification which incorporates the polyether segment into the chain at a late stage in the reaction.

The molecular weight and molecular weight distribution of PEO/PET copolymers were determined using gel permeation chromatography (g.p.c.). Two columns of 10^5 and 10^3 Å Styragel® were used with chloroform solvent at 25°C at a flow rate of 1 ml/min. The calibration procedure for PEO/PET compositions is described in detail elsewhere[7].

Typical g.p.c. data are shown in *Table 3.*.

Over a period of years, 12 batches of various PEO/PET compositions over the PEO range 50–70 wt % based on PEO 1500, were synthesized. $\bar{M}_n$ varied between 11 and 17 x 10^3, $\bar{M}_w$ 48–70 x 10^{-3} and $\bar{M}_w/\bar{M}_n$ was typically 4–6. Materials based on PEO 600 showed more variation in molecular parameters from batch to batch mainly due to variations in the low MW tail of the MWD. No work was carried

out on the 70/30 PEO/PET composition based on PEO 600 as the material was waxy and non-film forming.

The morphology of the three compositions was studied by X-ray diffraction and differential scanning calorimetry (d.s.c.). X-ray studies showed the presence of low levels of PEO and PET crystallinity indicating a two phase system. The 60/40 composition had an optical clarity that was absent in the 50/50 and 70/30 compositions. The family of materials was studied by d.s.c. at a standard heating rate of 10°C/min. A typical thermogram is shown for a 50/50 composition in *Figure 5*. The data for the series are summarized in *Table 4*.

When melted and quenched the materials in the 50–70 wt % PEO range were amorphous, however PEO crystallization occurs rapidly between −60 and −40°C. The PET domains crystallize over the 50–150°C range and these domains are the major reason for the mechanical properties. The length of the segments ~50 Å would suggest sandwich type domains rather than spherulite, but we have as yet no direct evidence for domain geometry of these materials. The materials are thermoplastic, the melting point being a function of the melting characteristics of the PET domains, and are thermaly stable under nitrogen to above 400°C, as shown by thermo gravimetric analysis (t.g.a.) at a heating rate of 20°C/min.

Tensile property measurements were made on microtensile test specimens cut from 500 μ films and measured using a Howden tensile testing machine. Typical stress/strain curves as a function of composition are shown in *Figure 6*. The results show a change in the mechanical properties of these materials as a function of composition. The 60:40 composition has the optimum properties, which are com-

Table 4 Thermal analysis data for bulk PEO/PET copolymers

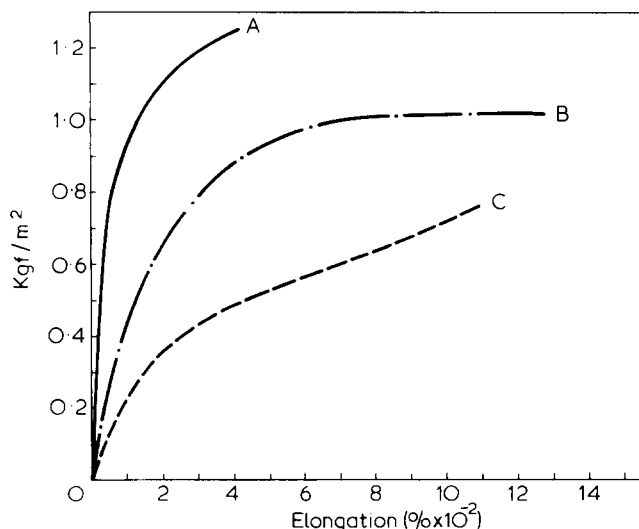| wt % composition (PEO/PET)	MW PEO	PEO T_g °C	PEO melt °C	T_m PET °C	$T_{decomp.}$ °C
48/52	1100	−60	7	230	480
57/43	968	−60	7	230	480
66/34	836	−60	7	230	480

Figure 6 Mechanical properties of PEO/PET copolymers as a function of copolymer composition. A, 50/50; B, 60/40; C, 70/30 wt % PEO/PET composition
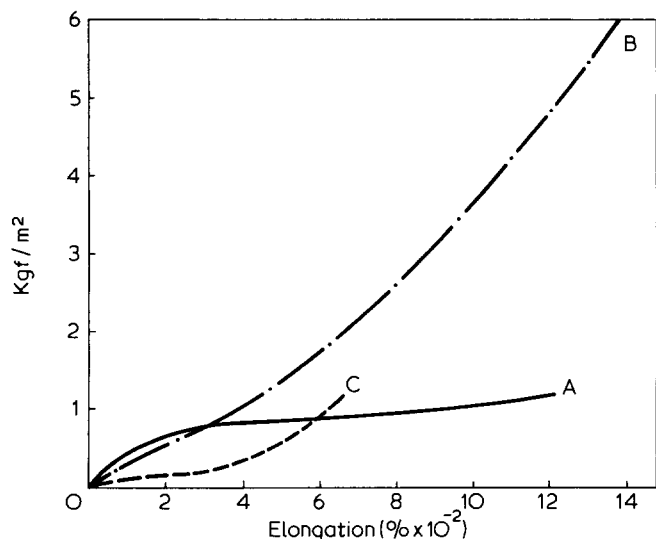
Figure 7 Mechanical properties of 60/40 PEO/PET (A) copolymers compared to Biomer® (B) and Silastic® (C)

Table 5 Equilibrium water contents for PEO/PET copolymers

wt % composition PEO/PET	MW PEO	Equilibrium water content % dry weight
48/52	1100	69
57/43	968	87
66/34	836	137

pared with polydimethyl siloxane and Biomer® (Medical Grade Lycra®), a standard polyetherurethane urea used in cardiovascular applications, in *Figure 7*. 60/40 PEO/PET copolymers have similar low extension properties to the Biomer® polyurethane, with a similar tensile strength to the medical grade silicone. Creep of the 60/40 material is serious above 200% elongation, but for low extension applications, i.e. <50% strains, the 60/40 composition has ideal properties for composite structures with polyether urethanes.

As PEO is hydrophilic, and these materials are to be used as biodegradable elastomers in the physiological environment, the equilibrium water contents were measured at 37°C. These are summarized in *Table 5*.

The results show that equilibrium water contents increase with PEO content, but that the incremental increase is dramatic above 60 wt % PEO. This coincides with the discontinuity of mechanical properties as a function of composition at 60 wt% PEO and suggests that above 60 wt%, PEO becomes the continuous phase.

CONCLUSION

A range of PEO/PET copolymers has been synthesized and their structures characterized and found to be close to those expected in theory. The individual copolymers have a narrow range of compositions. The mechanical properties have proved to be useful for certain medical applications, and the 60/40 composition appears to be optimum for use in composite structures with current medical elastomers, i.e. polydimethyl siloxanes and polyetherurethane ureas. The characterization methods have been developed and the baseline properties elucidated. We are now in a position to study the degradation of these materials both from mechanistic and applied viewpoints in the physiological environment. This will be described in Part II[8].

ACKNOWLEDGMENT

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