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New approaches to mapping through-thickness variations in the degradation in poly (lactide-co-glycolide)

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ABSTRACT

Biodegradable poly (lactide-co-glycolide) (PLGA) copolymers have been used for many years for biomedical applications such as soluble sutures, orthopaedic implants and more recently as potential tissue scaffold materials. The rate at which the copolymers degrade can be manipulated from a period of days to months by changing the lactide/glycolic acid ratio. Degradation of PLGA copolymers occurs by hydrolysis of the ester bonds in the polymer backbone. The hydrolysis reaction is autocatalytic and is accelerated by the build up of degradation products in the bulk of the material. As a consequence, material degradation is expected to be non-uniform through the specimen thickness with the material at the centre degrading at a faster rate than at the surface. Despite many studies of PLGA degradation, information on this local variance is sparse as the techniques used to track the process are usually bulk measures. In this study, two new approaches for monitoring degradation have been developed that enable *local* measurements of degradation to be made throughout the specimen over an extended period of time. Chemical and mechanical variations in the structure of the polymer have been mapped using attenuated total reflectance infrared spectroscopy (ATR-FTIR) and nanoindentation. These have produced comparable results and show that the degradation rate at the centre of the specimens is almost an order of magnitude higher than at the surface.

1. Introduction

The polyesters, poly (lactic acid) (PLA) and poly (glycolic acid) (PGA) as well as their copolymers, the poly (lactide-co-glycolide)s, PLGA's are widely used in healthcare applications, e.g. soluble sutures, orthopaedic screws and as potential tissue scaffold materials [1–4]. These materials degrade through hydrolysis of the ester linkages within the polymer backbone to form lactic and glycolic acids respectively, which can be naturally removed from the body [5]. The hydrolysis reaction is autocatalytic, i.e. the bulk material degrades at a faster rate than the surface due to a build up of carboxylic acid end groups [6]. The hydrophilicity of PLGA changes with the number of monomers that form the polymer chain. Oligomeric PLGA, which contains less than eighteen or so monomers, is hydrophilic and therefore water-soluble: the converse is true for longer chains [7]. As a consequence, the mass of a degrading sample of PLGA in a fluid bath remains constant until the chain lengths reach the hydrophilic oligomer stage at which point they are able to diffuse out of the material into the surrounding medium [8].

There have been many studies on the degradation behaviour of PLGA and its constituent polymers [5,7–11]. In general, these track changes in the number average molar mass (Mn) and mass average molar mass (Mw) and/or changes in mechanical performance with time and/or temperature. Infrared spectroscopy has also been used to monitor changes in the intensity of molecular vibration modes that are sensitive to degradation [12] e.g. ester bonds. This type of information is valuable as it can be used to confirm the autocatalytic nature of hydrolysis [13], exploit the phenomenon of time–temperature superposition in accelerated tests, or predict product lifetimes [8]. However, the data obtained is a global measure of degradation and provides no indication of local variation in the degradation rate. In that sense, the information obtained is effectively smeared over the different levels of degradation that occur through the thickness of a sample due to autocatalysis. In this paper, we describe two new approaches to monitoring the local degradation of PLGA are described. This information provides a more accurate representation of the temporal and spatial changes that occur with degradation time. Such data can be used to design better implants by incorporation into finite element analysis and analytic analysis software.

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2. Experimental

2.1. Materials and specimen preparation

The polymer specimens used in this study were produced from 85:15 poly (DL-lactide-co-glycolide) (polymer grade: PURASORB PLG 8523 produced by Purac Biochem, Gorinchem, Netherlands). Dried granules of PLGA were injection-moulded using a Minijet moulding machine into cylindrical rods (50 mm long, 8 mm in diameter) using a single-cavity, end-gated mould. The moulding conditions used are given in Table 1. After cooling the rods were cut into 10 mm long sections. These were then vacuum dried and sealed in foil bags in a dry environment and refrigerated at 4 °C.

2.2. Degradation testing

In vitro accelerated degradation tests were conducted according to the procedure outlined in ISO 15814 [14]. Specimens were placed in individual containers and fully submerged in 120 ml of phosphate-buffered solution (PBS, pH 7.4) with a solution to specimen ratio greater than 30:1. The containers were sealed using a screw top cap and placed upright into a water bath at 37 °C.

Specimens were removed in batches of three from the water bath at regular time intervals (3, 10, 15, 25, 35 days), washed with deionised water and wiped dry with a tissue. The specimens were weighed, and the surface chemical and mechanical properties determined using the methods described below. Subsequently the moisture content and loss of polymer were determined, after vacuum drying to constant weight. Finally, small samples (~5 mg) were taken from the specimens to determine the molecular mass profile at different positions with the specimens.

Through-thickness properties were determined for 3 specimens exposed to PBS solution for 3 days at 37 °C. Once tissue dried the specimens were sectioned by milling away approximately half the specimen length, leaving an exposed cross-section, Fig. 1. Milling was carried out using water as a coolant, the milling speeds and cutting tools were chosen to minimise any adverse effects due to heating. Indentation tests were conducted on the moulded surface and the machined cross-section close to it, to ensure that the milling process had not affected the polymer properties. The chemical and mechanical properties of the exposed cross-section were then determined to obtain a through-thickness profile.

2.3. Moisture content and polymer mass loss

Moisture uptake into the specimens was determined by weighing tissue-dried samples removed at specific time intervals during the degradation test from the water bath. The mass was then re-measured after the specimens had been vacuum dried to constant weight at 25 °C. The moisture content in the specimens is expressed as follows:

$$\text{Moisture content}(\%) = \frac{m_m - m_d}{m_d} \times 100\% \quad (1)$$

Table 1
Injection moulding conditions used to produce specimens.

Cylinder temperature	185 °C
Mould temperature	35 °C
Injection pressure	84 MPa
Injection time	10 s
Post hold pressure	42 MPa
Post hold dwell time	5 s

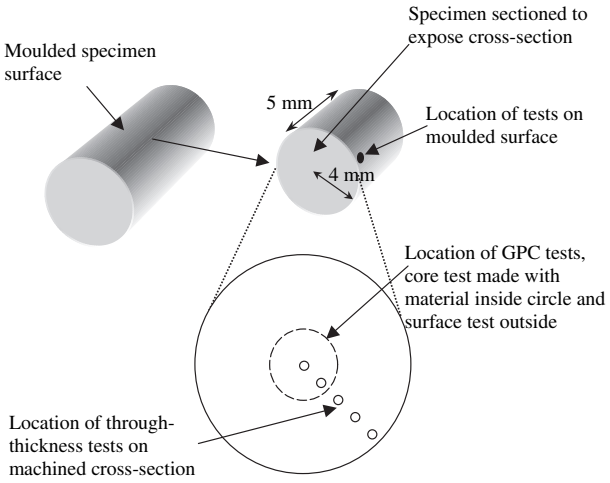

Fig. 1. Milling of a PLGA specimen to obtain an exposed cross-section suitable for through-thickness measurements. Chemical measurements were made at 1 mm intervals across the exposed cross-section indicated by (○), mechanical measurements were made at the same location at 0.2 mm intervals. Location of tests on moulded surface indicated by (●).

where: m_m = mass of *moist* specimen *before* vacuum drying and m_d = mass of a vacuum dried specimen.

Values for the mass of polymer lost from each specimen during the degradation tests were obtained from the following equation:

$$\text{Mass loss}(\%) = \frac{m_i - m_d}{m_i} \times 100\% \quad (2)$$

where: m_i = initial dry mass of a specimen before testing.

Mass measurements were made with a high precision balance (Mettler AT20) with a 10 μg resolution.

2.4. Nanoindentation

Indentation modulus was determined using an MTS-Nano Instruments nanoindenter, which is shown schematically in Fig. 2. The geometry of the three-sided pyramidal diamond indenter tip, known as a Berkovich indenter, was determined using atomic force microscopy. Load-control was achieved using the coil-magnet assembly that controls the shaft on which the indenter tip is

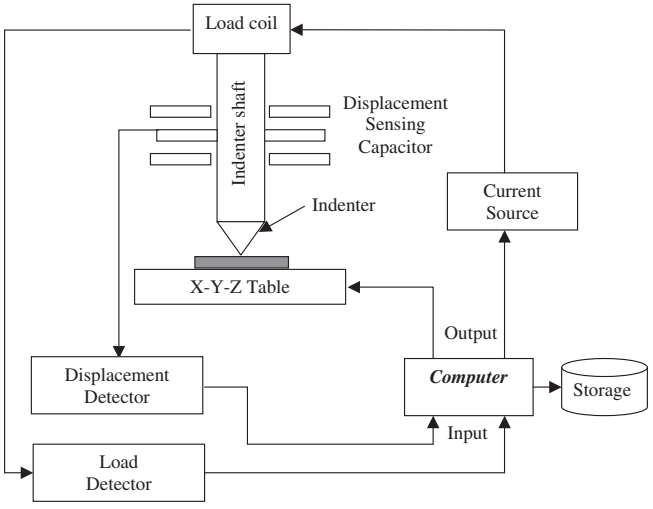

Fig. 2. Schematic diagram of the nanoindenter.