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Accelerated ageing and degradation in poly-L-lactide/hydroxyapatite nanocomposites

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ABSTRACT

Dry, compression molded films of medical grade poly-L-lactide (PLLA) showed a marked reduction in tensile strength and strain after accelerated ageing in aqueous NaOH at 50 °C, accompanied by mass loss, surface erosion, increased hydrophilicity and, in the case of the initially amorphous films, cold crystallization owing to the plasticizing effect of the ageing medium. Addition of well dispersed nanosized hydroxyapatite (nHA) particles resulted in increases in the rate of mass loss during ageing, identified with accelerated degradation at the matrix/particle interfaces. However, the associated decreases in tensile strength and strain to fail with ageing time were far less marked in the presence of the nHA than in the unmodified films. This implied that nHA acts as an effective toughener of the bulk material, consistent with TEM observations of the deformed films, which indicated failure of the particle–matrix interfaces to promote plastic deformation of the PLLA.

1. Introduction

Poly-L-lactide (PLLA) is a semicrystalline thermoplastic that is widely used in biomedical applications, owing to its excellent biocompatibility and inherent biodegradability [1–12]. It is currently under consideration for use in porous biodegradable scaffolds for bone repair, whose rate of resorption *in vivo* should ideally match the growth rate of the bone tissue, so that the overall structural integrity of the system is maintained [13,14]. The principal degradation mechanism of PLLA in aqueous media both *in vitro* and *in vivo* is hydrolytic de-esterification, which is reported to result in a progressive reduction in the bulk molar mass with degradation time under fixed conditions [15]. As degradation continues, soluble oligomers are leached from the surface, while those trapped in the interior increase the local acidity owing to the presence of carboxylic acid groups at the chains ends, which catalyze hydrolysis of the ester groups [15,16]. The oligomers are subsequently eliminated by natural pathways such as the tricarboxylic acid cycle and certain grades of PLLA have been approved by the US Food and Drug Administration for applications *in vivo* [14].

The rate of degradation of PLLA is reported to be dependent on factors such as its initial molar mass, purity, temperature, external dimensions and crystalline morphology [17–23]. Moreover, other physical changes may result from prolonged exposure to an aqueous medium, such as physical ageing, changes in the crystalline morphology and plasticization owing to water absorption, which may also be of crucial importance for the performance of PLLA *in vivo* [24–27]. There are conflicting reports on the effect of crystallinity on the resorption rate. For example, Tsuji et al. [19] found the degradation rate to increase with the initial degree of crystallinity in a buffer solution, and argued that a higher degree of crystallinity may result in a higher defect density in the amorphous regions, facilitating the penetration of water. On the other hand, the degradation rate has been reported elsewhere to decrease with the degree of crystallinity in both buffer solution and during accelerated ageing in alkaline solution [20,21,28].

A further consideration is the presence of filler particles, which is of particular concern in the context of PLLA-based biodegradable scaffolds, because addition of bioactive ceramic ("bioceramic") fillers, such as hydroxyapatite (HA), may potentially improve their osteoconductivity (the provision of a suitable substrate for bone growth on a surface, or into pores, channels or pipes [29]) [30,31]. A recent trend is to exploit the improved properties of polymer/bioceramic nanocomposites in which the modifier particles are of a similar size to those in natural bone, which consists essentially of around 60 wt% ceramic nanocrystals, comparable to HA in composition and structure, embedded in a polymer (collagen) matrix [32–35]. HA (nHA) nanoparticles (mean particle diameters of the

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order of, or less than 300 nm), for example, show enhanced osteoblast adhesion and surface deposition of calcium-containing materials with respect to HA microparticles (generally taken to refer to particles with diameters in the 0.7–700 μm size range), leading to enhanced osteoconductivity in the corresponding nanocomposites [36–38]. There are conflicting results on the effect of bioceramics on resorption rates. For example, Bleach et al. [39] and Niemelä et al. [40] reported unfilled PLLA to absorb more water and show greater mass loss than materials filled with tricalcium phosphate (TCP) microparticles, whereas other authors have observed increases in the degradation rate in the presence of HA or TCP microparticles, attributed to the particle/matrix interface and the hydrophilicity of the filler [41,42]. Moreover, there are relatively few results in the open literature on the effect of nanofillers such as nHA on the ageing and degradation behavior of PLLA, although increases in degradation rate have been observed in PLLA and similar materials in the presence of montmorillonite clay and oligomeric silsesquioxanes, for example [21,43,44].

The present work has therefore focused on the ageing and degradation of medical grade PLLA/nHA nanocomposite films with different degrees of crystallinity and different nHA contents, as a first step towards assessing the *in vivo* response of nanocomposite foam scaffolds based on supercritical CO_2 processing, currently under development in our institute, and in which additional factors linked to the foam morphology are also expected to play an important role [9–12]. In order to accelerate the ageing process for the purposes of this initial study, the tests were carried out in dilute alkaline solution at 50 °C (below the nominal glass transition temperature, T_g, of 60–65 °C for PLLA in the dry state). This procedure has been widely used in basic investigations of morphological and chemical changes during ageing [21,28,44–46], although it should be borne in mind that accelerated hydrolysis may not reproduce certain features of the ageing and degradation behavior of PLLA in a physiological medium at body temperature, the presence of an alkaline medium having been observed to promote surface erosion, for example [45].

2. Experimental

2.1. Materials

Bioresorbable poly(L-lactic acid) (PLLA, intrinsic viscosity 1.6 dL/g, from Boehringer Ingelheim, Germany), was provided in the form of flakes and dried overnight at 75 °C under vacuum prior to use. Previous gel permeation chromatography (GPC) studies of PLLA with comparable intrinsic viscosity have indicated a polydispersity of 1.5 and a weight average molar mass, M_w, of about 150,000 g/mol, which decreases by approximately 10 % after processing under conditions equivalent to those described below [47]. Hydroxyapatite nanopowder (nHA, nominal mean diameter < 200 nm from BET analysis, Sigma-Aldrich) was used without further purification or thermal treatment.

2.2. Processing

PLLA and nHA were compounded under dry nitrogen using a miniextruder equipped with twin conical co-rotating screws and a capacity of 5 cm^3 (DSM Micro 5 compounder, Netherlands). A screw rotation rate of 110 rpm, a temperature of 200 °C and a residence time of 4 min were used to prepare PLLA compounds containing 0, 5 and 10 wt% of nHA, which were subsequently stored at −18 °C (at higher nHA contents, it became difficult to introduce the dry mix into the extruder). The compounds were compression molded into 200 μm thick films (0.15 MPa for 10 min at 200 °C), using a bench-top press (Fontijne Holland, Netherlands). Processing under these conditions led to a uniform dispersion of approximately spherical nanometric nHA particles in the PLLA matrix as demonstrated in earlier work (90 vol% of the particles had a diameter less than 980 nm and 50 vol% had a diameter less than 360 nm [48]). The films were then subjected to different heat treatments depending on whether amorphous, partially crystallized or fully crystallized specimens were required. After conditioning at 200 °C for 10 min, the films were generally either (i) quenched in water at 15 °C to give an amorphous structure or (ii) annealed at 110 °C for 10 min and then quenched at 15 °C to give a fully spherulitic structure. A number of films were also annealed at 130 °C for 8 min (pure PLLA and PLLA/5 wt% nHA) or for 6 min (PLLA/10 wt% nHA) and then quenched at 15 °C to give a partially spherulitic structure. Different crystallization temperatures were used to obtain the partially and fully spherulitic films because the global solidification rate at 110 °C was too high for it to be possible to obtain partially spherulitic films under controlled conditions, whereas the slow crystallization rates at 130 °C resulted in excessively long times for complete solidification and hence the possibility of significantly increased thermal degradation.

2.3. Ageing treatments

Three 25 mm diameter discs were prepared from the films for each composition, annealing treatment and ageing time. These were weighed and placed in identical flasks containing 50 ml of 0.01 M NaOH in distilled water (pH 12). The flasks were left in the same oven at 50 °C. After the required ageing time, the specimens were removed from the flasks, washed three times in distilled water, and vacuum dried for 1 week at room temperature prior to characterization. The pH of the ageing media was monitored once a week using a pH meter (MP120, Mettler-Toledo, Switzerland). The maximum ageing times were five weeks, after which certain specimens became too brittle for mechanical testing.

2.4. Characterization

Weight loss and water absorption of the aged films were evaluated by weighing. The weight loss was calculated from:

$$\text{Weight loss } [\%] = 100 \times \frac{W_d - W_i}{W_i} \tag{1}$$

where W_d and W_i are the weights of the dried aged and unaged specimens, respectively. The water uptake was calculated from:

$$\text{Water uptake } [\%] = 100 \times \frac{W_w - W_d}{W_d} \tag{2}$$

where W_w is the weight of the film measured after wiping away any excess surface water.

Wettability was evaluated by contact angle measurements with deionized water using a video-based optical contact angle measuring system (OCA35 DataPhysics Instruments GmbH, Germany), before and after ageing. To measure the water contact angle, a sessile drop method was used, in which the advancing contact angle is determined a few seconds after a water drop is brought into contact with the surface to allow it to stabilize. A water drop of approximately 3 μm in volume was placed on the surface using a computer-controlled actuator. The contact angle was then determined from images taken at right-angles to the surface. All experiments were carried out under atmospheric conditions and at room temperature.

Modifications of the surface morphology were monitored by scanning electron microscopy (SEM, Philips XL30) at a tension of 3 kV in secondary electron mode. The films were coated with carbon to minimize charge accumulation and beam damage. The