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Swelling and hydrolytic degradation of poly(D,L-lactic acid) in aqueous solutions

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Abstract

Low molecular weight poly(lactic acid) was synthesized by direct polycondensation of lactic acid. The oligomers were characterized by viscometry, light scattering, and gel permeation chromatography (GPC). The swelling behaviour of tablets made of the above polymer immersed in buffer solutions at 37 °C was studied. In the same experiments, the hydrolytic stability of D,L-PLA was assessed by measuring the weight loss after drying the tablets. In order to inhibit any degradation due to bacteria, formaldehyde was added in the solution as biostatic factor. The effect of an incorporated drug on the swelling behaviour of D,L-PLA tablets was also considered. It was found that the incorporation of drug in D,L-PLA tablets increases their swelling index, probably due to the creation of additional porosity in the specimens or other interaction between drug and polymeric matrix.

Keywords: Poly(D,L-lactic acid); Swelling; Hydrolysis; Erosion; Degradation

1. Introduction

Degradable biomedical polymers are an interesting class of materials that can decompose to non-toxic products and find interesting medical and pharmaceutical applications. Typical products of this class are polymers deriving from polycondensation of lactic, glycolic and hydroxybutyric acids, and ε-caprolactone. These polymers are quite useful because they decompose via direct hydrolysis of the ester bond in an aqueous environment and give readily-absorbable degradation products [1,2].

Poly(D,L-lactic acid) (D,L-PLA) is an amorphous polymer with glass transition temperature 58 °C and a wide range of melting temperatures depending on its molecular weight. Two methods are currently available for PLA synthesis: low molecular weight polymers are obtained by step-growth polymerisation of lactic acid whereas high molecular weight polymers are synthesized by ring-opening polymerisation of lactide, which is the cyclic diester of lactic acid.

The hydrolytic degradation of these materials in aqueous solution proceeds through random cleavage of the ester bond. This process is controlled by four basic parameters: the rate constant, the amount of absorbed water, the diffusion coefficient of chain fragments within the polymer and the solubility of degradation products [3].

The degradation of a solid polymer matrix can proceed through two alternative mechanisms: (i) surface or heterogeneous, and (ii) bulk or homogeneous erosion [4]. In the case of surface eroding matrices, the polymer degradation is much faster than water intrusion into the polymer bulk. Degradation occurs, therefore, mainly in the outermost polymer layers and not in the inner parts of a matrix. Bulk eroding polymers, in contrast, degrade slowly and water uptake by the system is much faster than polymer degradation. Thus the entire system

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is rapidly hydrated and the polymer chains are cleaved throughout the device. However, it should be noted that all degradable polymers can erode via both pathways when the erosion conditions or the geometry are chosen appropriately.

The hydrolytic degradation of bulk, amorphous poly(D,L-lactic acid) devices was shown to proceed heterogeneously and to go faster in the inner part than at the surface, because in the interior there is a larger contribution of auto-catalysis [5]. Initially, hydrolysis of ester bonds proceeds homogeneously through the matrix. As degradation proceeds, the following two factors attain prime importance: (a) degradation causes an increase in the number of carboxylic acid chain ends which are known to autocatalyse ester hydrolysis, and (b) only oligomers which are soluble in the surrounding aqueous medium, can escape from the matrix. As degradation goes on, soluble oligomers, which are close to the surface can be leached out before they are fully degraded, whereas those which are located in the core of the matrix remain entrapped. This leads to a low pH in the core which in turn, results in the acceleration of degradation.

The degradation of semi-crystalline PLLA matrices proceeds in an even more complicated way. Fischer et al. [6] reported that hydrolytic degradation proceeds in two stages. During the first stage, water diffuses into the amorphous regions resulting in random hydrolytic scission of ester bonds. The degree of crystallinity can even increase as degradation proceeds. The second stage starts after degradation of the major part of the amorphous area. The hydrolytic attack proceeds from the edge towards the centre of crystalline domains.

de Jong et al. [5] studied the hydrolytic degradation of monodisperse lactic acid oligomers. They concluded that at low pH values, hydrolysis proceeds by chain-end scission whereas in alkaline media, lactoyl lactate splits off. The OH end group was found to play a crucial role in the hydrolytic degradation; when OH was blocked no significant degradation was observed.

A kinetic equation to describe the autocatalytic effect of the increasing carboxyl acid end-group concentration was presented by Siparsky et al. [7], who studied the hydrolysis of PLA in aqueous acetonitrile solutions.

Additional parameters that influence hydrolysis are the temperature and pH of the solution [8–10]. The mode of scission during hydrolysis of biodegradable polymers could be completely random regarding the backbone bonds or it could follow a ''chain-end-unzipping'' mechanism. It was found that the base catalysed hydrolysis of D,L-PLA proceeds via a random process, while the acid catalysed hydrolysis follows a fast chain-end scission [9].

It was also established that the hydrolysis rate is higher in acidic than in neutral media [8]. Schliecker et al. [3] synthesized D,L-lactic acid oligomers and studied their degradation. The hydrolytic rate was dependent on the molecular weight of the oligomer, the temperature and pH of the media, with the lowest rate found around pH 4.5. Under acidic conditions the mode of reaction was chain-end cleavage, whereas under basic conditions degradation of oligomers proceeds via random ester cleavage.

Degradation becomes a bulk process above T_g, while at temperatures below T_g degradation of the polymer matrix is restricted to its surface [10]. Hausberger et al. [11] studied the influence of gamma-irradiation on biopolymers and they reported that the onset times for degradation decreased with increasing irradiation dose.

The progress of polymer degradation is assessed by measuring the weight loss of the sample, in a microbalance within a selected time interval, by determining the molecular weight reduction of the polymer by means of gel permeation chromatography (GPC) or by assessment of the M_w from the intrinsic viscosity [1]. A qualitative graphical method was also developed for studying the mode of the hydrolysis of biodegradable polymers. This approach requires the determination of the molar fraction of the monomer by nuclear magnetic resonance (^{1}H NMR) or high performance liquid chromatography (HPLC) as well as the degree of degradation by ^{1}H NMR [9]. Differential scanning calorimetry (DSC) is another method suitable for determination of the T_g that might be a measure of the polymer degradation [10].

PLA decomposes to its monomer, lactic acid, which is a normal metabolite of the human body. This behaviour makes this polymer suitable for many important biomedical uses such as the preparation of resorbable sutures, production of implants for orthopaedic surgery or blood vessels etc. Very interestingly, PLA has been used in the sustained release of drugs, for the delivery of antimycobacterial drugs, quinolones, antimalarial and antiinflammatory drugs, antitumor agents and hormones and has been the base of fluoride containing tablets for oral use [12–14].

It is evident that degradation of PLA is very critical for drug delivery behaviour in the controlled release systems based on this polymer. In fact, the already reported surface and bulk erosion combined with the autocatalytic effect of carboxyl groups probably disturb an even rate of release and more specifically, the status of zero order release, which is desired when designing the above systems [15]. Furthermore, the drug diffusion through the polymeric matrix is an additional mechanism contributing to the complexity of the phenomenon. This latter mechanism is obviously influenced by the swelling characteristics of the polymeric matrix. Therefore, the study of stability of PLA specimens immersed in various aqueous media seems to be important as a means of providing useful information to further explore the performance characteristics of biodegradable controlled release systems.

The interactions between matrix and drug are another critical parameter which influences the drug delivery systems. The chemical interactions between the entrapped compounds and the biodegradable polymer may have a strong effect on polymer degradation and the drug release [16]. Neutral drugs can either catalyse or retard the polymer degradation rate. In particular a hydrophobic drug tends to restrict water uptake and thus decreases the degradation rate, while a hydrophilic drug has an opposite effect on the water uptake and degradation rate. For acidic drugs, one can expect faster hydrolysis of ester bonds because of acid catalysis. In contrast, in the case of basic drugs two effects can be observed: base catalysis of ester