The effect of hydrolytic degradation on the tensile properties of neat and reinforced Poly(p-dioxanone)

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Summary

In this work a bioabsorbable Poly(p-dioxanone), PPDX, was mixed with 5 and 20% by weight Hydroxyapatite (HA) or Boron Nitride (BN). Pins of neat and filled PPDX were molded by a compression and transfer process. The pins were subjected to tensile testing before and after hydrolytic degradation. The hydrolysis was performed in vitro using a pH 7.4 phosphate buffer solution at 37 ºC during 8 weeks. The use of 5% HA had almost no effect on the elastic modulus of PPDX, while 20% caused a slight reduction of this property. These results are probably related to poor dispersion and minor degradation of the matrix catalyzed by HA. Samples with HA were degraded much faster by hydrolysis than neat PPDX. On the other hand, the elastic modulus of PPDX was highly improved by the presence of BN, 5% of this compound increased its value from 35 MPa to 110 MPa, while 20% BN raised it to 160 MPa. Additionally, the value of the elastic modulus of PPDX/BN samples decreases with hydrolytic degradation time but is higher, after 8 weeks degradation, than that of neat PPDX. These are interesting results from the application point of view, since the reported values for the elastic modulus of the trabecular bone are in the range 50-100 MPa and therefore the BN filled PPDX may be useful for bone fixation implants.

Keywords: Poly(p-dioxanone), hydrolytic degradation, trabecular bone, boron nitride, hidroxyapatite.

Introduction

The hydrolytic degradation of many bioabsorbable biopolymers has been the subject of several recent studies. In particular, the chemical changes and the effects of degradation on the crystallinity and molecular weight and its distribution have been reported for degradative processes "in vivo or in vitro" [1-6]. Unfortunately, these physical properties cannot generally be used to make quantitative predictions about the change in mechanical properties during the degradation of the polymer [7].

Polymers that undergo hydrolytic degradation are known to suffer losses in their mechanical properties that are usually monitored by a decrease in their elastic

modulus as degradation proceeds [6,8]. In semi-crystalline biodegradable polymers a complex interplay between variations in molecular weight, morphology and crystallinity difficult lifetime prediction and mechanical properties loss during degradation [1-7]. Another factor that must be considered is the shape and size of the polymer submitted to hydrolytic degradation since the processing of the material as well as the associated thermal history may be very important in order to generalize the results, especially for "in vivo" applications.

For medical applications (e.g., fracture fixation) a desirable material for implant should provide initial mechanical strength to the injured area, induce or allow new bone growth, and degrade systematically into nontoxic re-absorbable compounds. The focus of this study was to examine the influence of hydrolytic degradation on the mechanical properties of a bioabsorbable polymer, the poly(ester-ether) Poly(p-dioxanone), PPDX, whose chemical repeat unit is:

$$-(- CH_2 - CH_2 - O - CH_2 - \overset{\overset{\textstyle O}{\|}}{C} - O -)_n-$$
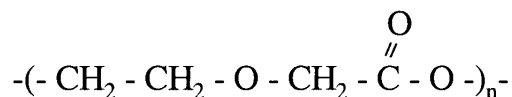
The material was studied both without modification and reinforced with two different types of fillers.

Experimental

The PPDX used in this work was Orthosorb by Johnson & Johnson. The material was mixed with 5 and 20% Boron Nitride (BN) and with equal amounts of Hidroxyapatite (HA). The mixing was performed manually with a glass rod on a glass slide placed on a hot plate, while the temperature was monitored with a contact thermocouple. The homogeneity of the dispersion was checked by Polarized Optical Microscopy and found in most cases to be very good.

Both neat and reinforced PPDX were molded by a compression and transfer process at 140 ℃ into pins (30 mm in length and 1.5 mm in diameter) that were later used to determine tensile properties. The compression and transfer device, as well as the mold, were designed and constructed by the Prototype Laboratory of the Mechanical Engineering Department at Simón Bolívar University. The homogeneity of the molded pins was verified by performing cryogenic fracture of specimens at different points and corroborating the lack of pores and cavities with an Optical Microscope.

The in vitro hydrolytic degradation was performed using a buffer solution. The 0.2 M buffer solution of pH 7.4 was prepared from hydrogenated sodium phosphate Na_2HPO_4 and di-hydrogenated potassium phosphate KH_2PO_4. The pins were subjected to a hydrolytic degradation process at a constant temperature of 37 °C during 8 weeks, a time after which some of the samples were so deteriorated that it was impossible to manipulate them without provoking a brittle fracture (see results). Samples were periodically removed from the hydrolysis medium, during the first two weeks every 3 days, and later on every week. Then they were dried until they achieved a constant weight using a vacuum oven at room temperature.

Thermal analysis was performed with a Perkin-Elmer DSC-7 under an ultra-high purity nitrogen atmosphere. The equipment was calibrated with indium and tin standards. Sample weight was kept constant at 5.0 mg. Heating and cooling scans

were recorded at 10°C/min. The efficiency of nucleation was analyzed according to the work of Fillon et al. [9-10]. The morphology of neat and reinforced PPDX was studied with a Zeiss MC-80 polarizing microscope (PM). A Vitrodyne V1000 universal testing machine was used to perform uniaxial tension tests in the pins before and after a specific degradation time. The strain rate used was 0.5 mm/s and at least 10 identical pins were used to obtain average values of the measured properties.

Additionally, the viscosity average molecular weight of neat and degraded samples was determined by the use of capillary viscometry of dilute solutions of the polymer in phenol/tetrachloroethane [6]. The surface morphology of degraded PPDX samples was observed with a Scanning Electron Microscope (Phillips, model SEM 505), the samples were sputter-coated with gold/palladium in a metal plating equipment (Balzars, model SCD 030).

Results and Discussion

Differential Scanning Calorimetry, DSC

Fig. 1 shows DSC cooling scans from the melt at a cooling rate of 10°C/min of PPDX after keeping it at 140°C for 5 minutes in order to erase its thermal history, of samples with and without different amounts of HA or BN.

The cooling scan of PPDX without nucleating agents (Fig.1.) exhibits a crystallization exotherm that peaks around 44 °C (see Table I). When BN is added to PPDX a clear nucleating effect can be observed by a substantial increase of the onset and peak crystallization temperatures (see Table I). The peak crystallization temperature (Tc) during cooling from the melt has been correlated with the nucleation density, and it has been shown that as Tc increases the number of nuclei per volume also increases [9,10]. Since Tc was increased, PPDX had more effective time to crystallize during the cooling scan and therefore the crystallinity achieved also increased when BN was mixed with the polymer as indicated in Table I. When 20% BN was used, the nucleating effect was saturated as demonstrated previously [11].

An opposite trend to that observed with the addition of BN occurs when HA was used. An apparent "antinucleation" effect was detected as signaled by the decrease in both the onset and peak crystallization temperatures when 5 % of the compound was incorporated in PPDX. Fig. 1 and Table I show that upon increasing the amount of HA up to 20 %, the "antinucleating" effect disappears and the peak crystallization temperature becomes closer to that of neat PPDX. The reason behind the antinucleating effect of HA on PPDX has been attributed to chemical interactions between PPDX and the phosphate groups present in HA (see Ref. [11]).

Changes in peak crystallization temperature during dynamic cooling runs from the melt can be interpreted as directly related to changes in nucleation density. This correlation has been shown before for other polymers and in this case measurements were made on the nucleation density of PPDX with and without nucleating agents by PM during isothermal crystallization and the results seem to be in accordance with the efficiency of nucleation as judged by Tc increases.

In order to rate the efficiency of the two nucleating agents used here, we have employed the efficiency scale proposed by Fillon et al. [10-11]. This nucleating efficiency (NE) allows a comparison to be made with self-nucleation, i.e., when the polymer has the maximum number of ideally suited nuclei (since they are crystal fragments of equal chemical constitution and identical crystal lattice as the polymer).
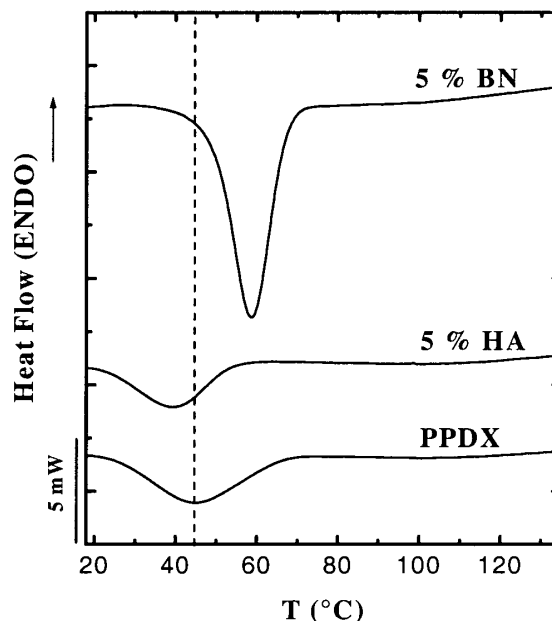
Figure 1. DSC cooling curves for neat and filled PPDX after erasing thermal history at 140°C for 5 min, cooling rate 10°C/min.

The expression of NE proposed by Fillon et al. [10], is:

$$NE = 100\frac{T_{cNA} - T_c}{T_{c\,max} - T_c} \tag{1}$$

where T_{cNA} is the peak crystallization temperature of the polymer with the nucleating agent to be evaluated, T_c is the crystallization temperature of the neat polymer and T_{cmax} is the optimum self-nucleation temperature of the neat polymer (i.e., the minimum temperature where self-nucleation will induce a maximum nucleation density without annealing of unmelted crystal fractions). A detailed explanation of the self-nucleation behavior of PPDX can be found in ref. [12].

The efficiency NE is expressed as a percentage where 0 represents no nucleating action and 100 would be the ideal nucleating action. Table I, shows the NE as a function of nucleating agent content for the two substances employed. The "antinucleation" effect of HA is now reflected in negative NE values that progressively increase as the HA content increases. For BN, an efficiency of 30 % was achieved when 5 % of the compound was added to PPDX and NE increased to 40 % when 20 % BN was used. In the BN case, the maximum NE is only achieved when the content is as high as in formulations where the compound would be considered a filler; on the contrary, with HA no apparent nucleating action could be detected in PPDX.

It is interesting to analyze the effects of the presence of nucleating agents on the maximum crystallinity achieved by PPDX during cooling from the melt, since this is a parameter that can influence the mechanical properties of the compounds and their hydrolytic stability.

Table I. Relevant thermal transitions and enthalpies during cooling at 10°C/min, determined by DSC for PPDX and PPDX with different contents of nucleating agents.

Filler	$Tc_{(onset)}$, °C	$Tc_{(peak)}$, °C	ΔHc, J/g	Xc, %	NE, %
0 %	55.3	43.8	35.1	25	0
5 % BN	67.3	58.7	60.8	42	30
20 % BN	68.5	62.2	60.1	42	40
5% HA	53.5	39.7	29.4	20	-10
20 % HA	55.4	43.0	41.6	32	-3

Table I presents crystallization enthalpy values taken from dynamic DSC cooling runs (such as Fig. 1) as a function of nucleating agent content. PPDX is a polymer that only crystallizes up to a value of approximately 25% crystallinity during cooling from the melt at 10°C/min, as indicated in Table I. Boron Nitride can sharply increase the crystallinity achieved by PPDX during cooling from the melt at 10°C/min. Even with 5% BN content the crystallinity increases to 42% (an increase of 68% with respect to the crystallinity obtained by neat PPDX). Such an increase in crystallinity will be reflected in an increase in both hydrolytic stability and tensile modulus of the material.

The behavior of PPDX with HA is also shown in Table I. The compound causes a reduction in PPDX cristallinity when 5 % is added. This is clearly a consequence of the reduction in Tc observed in Fig. 1, of approximately 4°C. It seems that the "antinucleating" effect delayed the onset of nucleation from the melt to such an extent, that the overall crystallinity achieved during cooling to 0° C was decreased. As the content of HA was increased to 20 %, both Tc and ΔHc recovered and increased to values close to that of neat PPDX. The reason why the "antinucleating" effect disappears as the content of HA increases is not clear but it may be related to the tendency of HA to form aggregates [11]. In formulations of PPDX/ HA, we were able to observe by PM large aggregates with sizes ranging from 50 to 100 μm [11] .

Effect of BN and HA on the Elastic Modulus of PPDX.

The mechanical properties of biomaterials, and the way they deteriorate during degradation, are very important to determine lifetime prediction of these materials. Figure 2a presents a comparison between the elastic modulus of neat PPDX with and without BN and HA. It can be seen that the addition of HA causes almost no effect on the elastic modulus, within the standard deviation of the measurements, when 5% HA is used. A small decrease in elastic modulus was observed for the material filled with 20% HA. This lack of effect, and even lowering of elastic modulus at higher HA content, is a fact that can be related to the antinucleation effect and to the poor dispersion of this agent on the PPDX matrix, as previously mentioned. The presence of HA agglomerates may act as stress concentrating particles that can negatively affect the mechanical properties of the matrix.

An additional factor that may be influencing the lack of improvement of the elastic modulus upon adding 20% of HA, could be that a small degradation effect of the PPDX matrix, catalyzed by HA, may be taken place during mixing. The PPDX is highly sensitive to hydrolytic degradation and even small traces of moisture can

trigger this process [6,13]. The mechanism of hydrolytic degradation of PPDX in the presence of HA involves the hydrolysis of the ester group, followed by the formation of a complex between the hydrolyzed PPDX and phosphate ions that may form on the surface of the HA particles (see ref. [11]). In order to test this hypothesis, samples containing HA were carefully dissolved in a mixture of phenol and tetrachloroethane and filtered twice to remove HA. Subsequently, intrinsic viscosity measurements were performed and the viscosity average molecular weight was determined. It was found that the value of $M_v = 2.20 \times 10^5$ g/mol for neat PPDX, decreased to 1.93×10^5 g/mol for the PPDX that was mixed with 5% HA and to 1.75×10^5 g/mol for the sample mixed with 20% HA. Although the decreased in Mv was small, it was measurable and well beyond the experimental error involved in the viscosimetry technique employed. Parallel experiments were performed for the samples containing BN and no change in Mv could be detected.

The addition of BN, on the other hand, notably increases the elastic modulus of PPDX and the effect is a function of BN content, like with reinforcing fillers. Such increase in elastic modulus is probably caused by a combination of the reinforcing action of BN and the increase in crystallinity that it produces on PPDX (Table I). Even though there was no change in crystalinity between the samples containing 5 and 20% BN, the elastic modulus still increased indicating that BN is acting like a reinforcing filler for PPDX. The fact that the dispersion of BN on the matrix was very good and its relatively high nucleating efficiency may also contribute to the improvement of the elastic modulus of PPDX, since the spherulitic size is substantially reduced [11,14] upon addition of BN. The much higher nucleation density produced when BN is added to neat PPDX, renders the morphology more homogeneous from a macroscopic point of view with less interspherulitic defects, a fact that is probably connected with the improved elastic modulus observed in Fig. 2(a) [11,14,15].

The effect of hydrolytic degradation on the elastic modulus of neat and filled PPDX is presented in Figure 2 (b). Here the catalytic effect of HA on the hydrolytic degradation of PPDX can be appreciated by comparing the relative reduction in the values of the elastic modulus, with the degradation time for the neat samples and those with HA. This Figure clearly shows how the decrease in elastic modulus during the first 20 days is much more pronounced in the samples with HA, even though they contain similar amounts of crystalline regions as compared to neat PPDX (Table I).

The loss of mechanical properties during hydrolytic degradation of biopolymers is well documented in the literature [4,7,8,15]. A group of factors may explain this behavior, among which the most important are: molecular weight loss, mass loss and associated morphological changes [1-6]. Fig. 2(b) also shows how the elastic modulus of neat and filled PPDX does not change much during the first 6 days of hydrolytic degradation.

The hydrolytic degradation process starts in the amorphous regions of the sample as a statistical process. During the first few days the extent of degradation is not so high as to produce low molecular weight soluble material. Therefore the morphological picture of lamellar regions that are connected through amorphous interlamellar regions with tie chains and entanglements, still holds and the mechanical properties are maintained. This result is also accompanied by an almost total lack of mass loss and pH changes during the first few days of hydrolytic degradation [6,13]. Additionally, observations performed on PPDX samples by Scanning Electron Microscopy indicated that the hydrolysis medium is diffusing radially, so that degradation progresses also radially. Therefore, during the first week of degradation

the samples will contain a core that is much less degraded than the external layers of the sample [6].
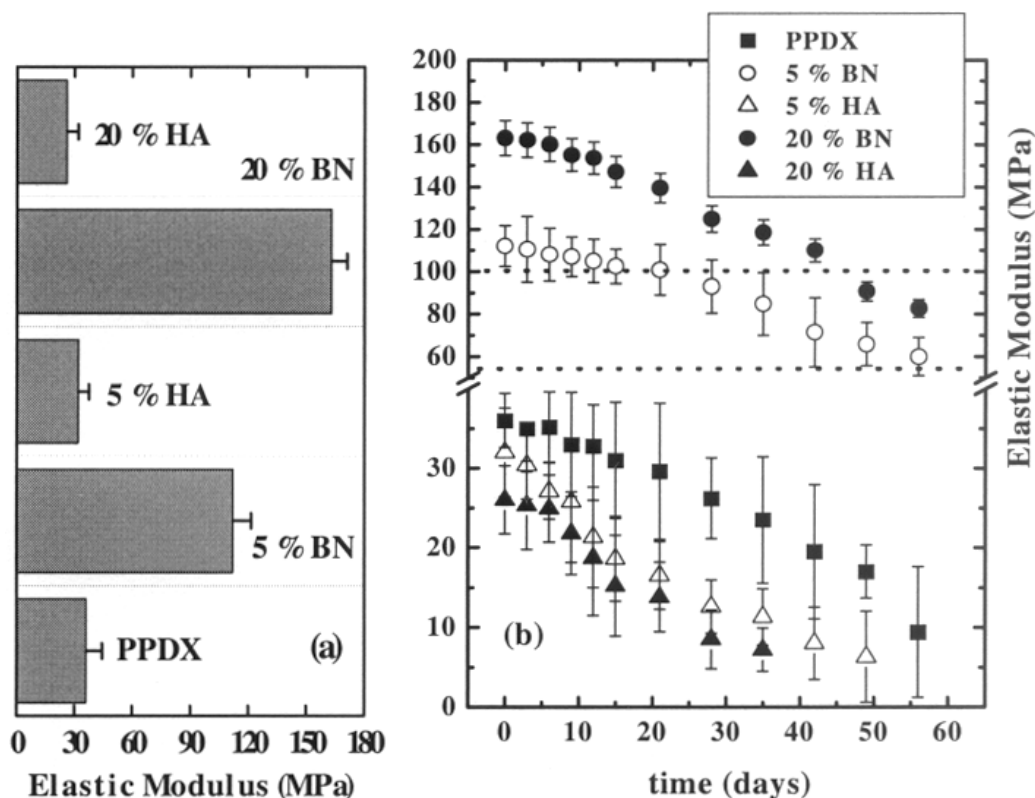

Figure 2. (a) Elastic Modulus for neat and filled PPDX. (b) Variations of Elastic Modulus with hydrolytic degradation time of neat and filled PPDX; the horizontal lines indicate the range of reported values of elastic modulus of the trabecular bone.

The elastic modulus values for trabecular bones range from 50-100 MPa, as schematically shown in Fig. 2 (b), while the cortical bone has much higher values of the order of 13.8 GPa [16], and from these two, the trabecular occupies a bigger internal area of the bone constitution. The fact that the elastic modulus of the materials examined does not change much during the first week of hydrolytic degradation can be highly beneficial from the application point of view. Fracture consolidation and bone callus formation, will probably need good mechanical properties of the bone fixation material during the first few weeks of the implant (i.e., 4-6 weeks [17]). The use of BN can increase the elastic modulus of PPDX to values higher than those exhibited by trabecular bones and the deterioration of this property with degradation time is also slower, see Fig. 2 (b). Therefore, the results suggest that the way the elastic modulus decays with degradation time and the actual values of the elastic modulus could be modified by an appropriate choice of BN content in a PPDX matrix. Other important parameters such as PPDX molecular weight and its morphology could well be tailored for a specific application.

In the case of HA, Fig. 2 (b) shows that the deterioration of the mechanical properties with degradation time is very fast as previously mentioned, therefore other

applications where rapid bioabsortion is needed may be envisaged for such a material. In fact, after 36 days of hydrolytic degradation, no data points are reported since the mechanical properties of the PPDX/20% HA samples were so brittle that they fractured when loaded on the mechanical testing equipment.

Conclusions

Boron nitride is an effective nucleating agent for PPDX that can also reinforce the material, thereby substantially increasing its elastic modulus. Only 5% of BN can raise the elastic modulus of PPDX from approximately 35 MPa to 110 MPa. Additionally, during hydrolytic degradation this material retains the value of the elastic modulus above 60 MPa even after 8 weeks of degradation. This may be interesting for bone fixation applications, since the reported elastic modulus of trabecular bone is in the range 50-100 MPa.

On the other hand, HA does not nucleate PPDX and can even cause antinucleation effects in view of its poor dispersion ability in a PPDX matrix. Furthermore, HA can catalyze the degradation of PPDX and does not improve its mechanical properties. During hydrolytic degradation the decrease in mechanical properties is very fast and the samples with HA do not possess mechanical integrity after 36 days of hydrolysis. Applications were fast bioabsortion of the material is desired may benefit from such a behavior.

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