Processing and properties of two different poly (ortho esters)

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Processing and properties of two structurally different poly (ortho esters) (POE) and their *in vitro* behavior have been compared. One POE was a copolymer of diketene acetal 3,9-diethylidene-2,4,8,10-tetraoxaspiro[5.5]undecane, *trans*-cyclohexanedimethanol and polyacetal. The other POE was a copolymer of diketene acetal 3,9-diethylidene-2,4,8,10-tetraoxaspiro[5.5]undecane, *trans*-cyclohexanedimethanol and *trans*-cyclohexanedimethanol-dilactide. The polyacetal POE was also used as a matrix incorporating two different model drugs, caffeine and furosemide. Both polymers were ultrasonically molded into slabs. The lactide modified POE was also melt-extruded into rods and self-reinforced using a solid state die-drawing technique. The initial strength values of both ultrasonically molded and extruded samples were close to those of non-oriented poly lactic acids. Self-reinforcing increased the shear strength, bending strength and modulus of the rods from 41.7 ± 1.7 MPa to 66.7 ± 2.3 MPa, from 78.5 ± 22.8 MPa to 183 ± 23 MPa and from 2.5 ± 0.3 GPa to 4.4 ± 0.3 GPa, respectively. *In vitro* hydrolysis of samples was studied either in phosphate buffer saline (PBS) or in simulated body fluid (SBF) at 37 °C. Samples degraded faster in unchanged PBS than in PBS changed weekly. The total *in vitro* strength retention time was relatively short varying from 14 days to 42 days depending on the processing method and polymer type. Samples retained their wet weight at initial level for a longer time but dry weight started to decrease already after the first *in vitro* week. Polymers or degradation products crystallized in SBF but remained amorphous when hydrolyzed in PBS. Some of the devices showed evidence of surface erosion, and the processing method affected the erosion. The storage time of these polymers was found to be limited. However, both polymers were found to be of interest in bone fixation and tissue engineering.

1. Introduction

Poly (ortho esters) (POE) have been extensively studied in controlled drug release applications [1]. POEs are very versatile and flexible: fast eroding polymers with low glass transition temperature (T_g) as well as rigid, more slowly eroding polymers with higher glass transition temperatures can be prepared [2]. POEs are amorphous and only one example of a crystalline polymer has been reported [3]. Polymers with higher T_g have a potential to be used in load bearing applications, such as fixation of small bone fractures.

For these applications, POEs have not been studied in great detail. Some POE-related processing studies and degradation studies related to processing have been published earlier. Processing has been reported by solvent casting the films using chloroform [4] or methylene chloride [5–9] as a solvent which in some cases have been stabilized with triethylamine. Films have also been made with hot-pressing [10]. POEs have also been compression molded to rectangular bars [11, 12]. POEs have also been reported to be processed by injection molding [11, 13, 14]. It has also been extruded [15] or melt-spun to monofilament [9]. The ultrasonic molding of polymers or polymer/drug devices has previously been reported [16–18]. However, in many cases processing strongly effects polymer's properties and behavior and thus those should be studied. Moreover, for example, film casting using harmful solvents is not a recommended nor commercially acceptable production method and other methods should be favored. Some reports about mechanical properties of either plates [5, 10, 19], films [5–7, 20] or slabs [16, 21] made of several POEs have been published.

In this study, processing and *in vitro* behavior of two structurally different POEs have been compared. One POE was a copolymer of diketene acetal 3,9-diethylidene-2,4,8,10-tetraoxaspiro[5.5]undecane, *trans*-cyclohexanedimethanol and polyacetal. The other POE was a copolymer of diketene acetal 3,9-diethylidene-2,4,8,10-tetraoxaspiro[5.5]undecane, *trans*-cyclohexanedimethanol and *trans*-cyclohexanedimethanol-dilactide. The polyacetal POE was also used as a matrix

incorporating two different model drugs, caffeine and furosemide. These were used in 2, 5 and 7 wt % concentrations in the matrix. Both polymers were ultrasonically molded into slabs. Additionally, the lactide modified POE-LA was melt-extruded to rods and self-reinforced using a solid state die-drawing technique. *In vitro* hydrolysis of samples was determined in either phosphate buffer saline (PBS) or simulated body fluid (SBF) at 37 °C. PBS was used both by changing and unchanging the solution. Mechanical properties (three-point bending and shear), thermal properties, weight change and structural changes were studied. The storage of extruded POE-LA was also studied.

Both these polymers were found to be interesting for bone fixation and tissue engineering applications.

2. Materials and methods

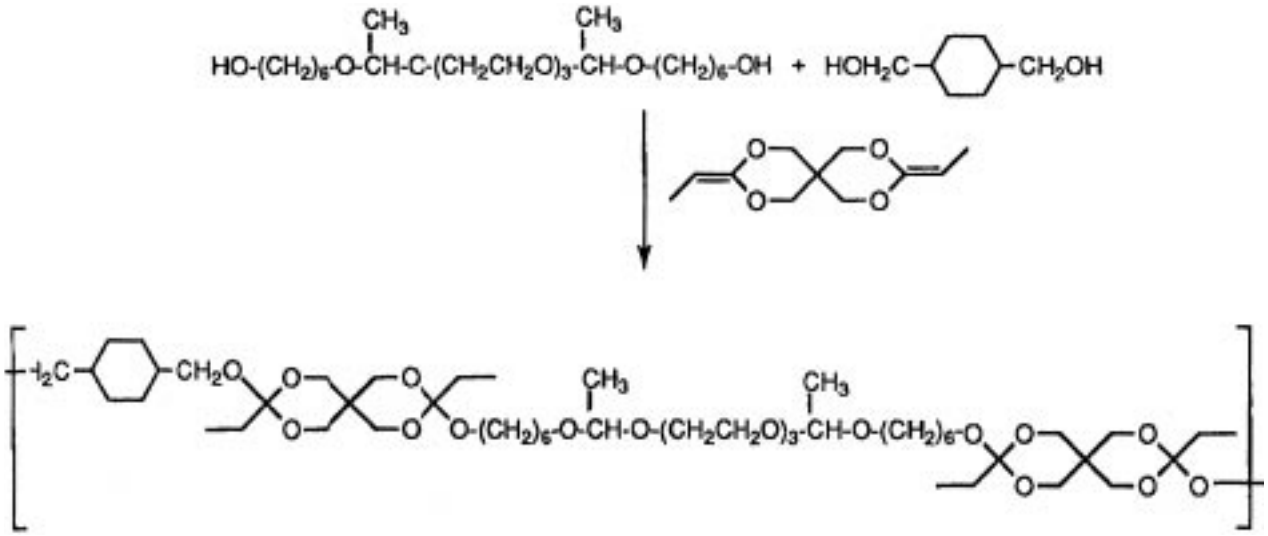
2.1. Materials

Two structurally different POEs were used in this study. The first POE was a copolymer of 90 mol % *trans*-cyclohexanedimethanol and 10 mol % polyacetal, (Fig. 1a) M_w 46 460, prepared as described in [3]. The glass transition temperature (T_g) was 32 °C and the decomposition temperature (T_d) was 275 °C as determined under nitrogen gas using thermogravimetric analysis. The polymer was processed neat and with two drugs, caffeine and furosemide (both supplied by Orion-Farmos, Finland). Both drugs were incorporated at 2, 5 and 7 wt %.

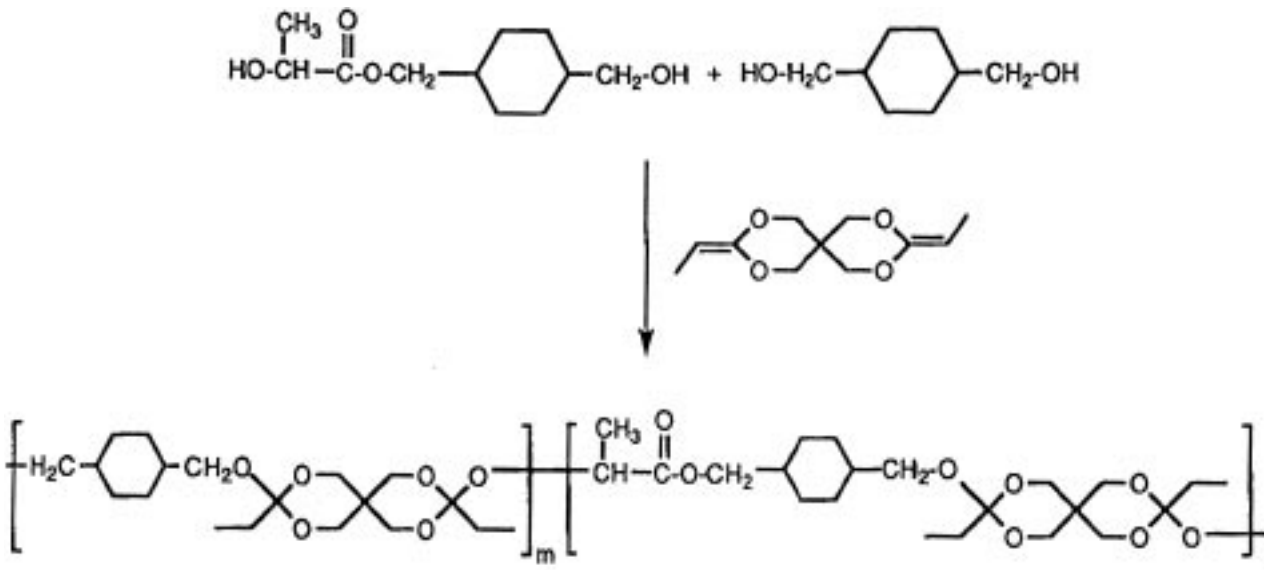
The second polymer (POE-LA) was a copolymer of 99 mol % *trans*-cyclohexanedimethanol and 1 mol % *trans*-cyclohexanedimethanol-dilactide (Fig. 1b), M_w 51 000, prepared as described in [11]. This polymer was only used neat. The glass transition temperature (T_g) was 102 °C and the decomposition temperature (T_d) was 342 °C determined under nitrogen gas by thermogravimetric analysis.

2.2. Specimen preparation and processing

Before processing, both polymers were ground to less than 1.0 mm particle size using a laboratory scale mill and liquid nitrogen cooling.



(a)



(b)

Figure 1 (a) Chemical structure of POE and (b) chemical structure of POE-LA.

Drugs were incorporated into the POE by mechanically mixing the polymer and drug. The powders were dried in a vacuum oven (2×10^{-2} torr) for 3 days at room temperature before processing. Both neat polymers as well as those containing caffeine and furosemide were fabricated into ϕ 11.5 × 2 mm slabs weighing 0.2 g each by ultrasonic molding (US) from slightly prepressed slabs as previously described [16]. The ultrasonic compressor used was a Rinco Ultrasonics PCS II apparatus used at 1.2–1.3 bar pressure for 0.19–0.28 s, depending on the material. Energies transmitted to the devices varied between 150 and 200 Ws. POE-LA powder used in the first extrusion (EX ... I) was dried for a total of 40 h of which 5 h were at 60 °C and 35 h at room temperature in vacuum. The POE-LA powder used in the second extrusion (EX ... II) was dried in vacuum for 24 h of which 2 h were at 110 °C and 22 h at room temperature before extrusion.

POE-LA was melt-extruded twice to form rods having a nominal thickness of 3.0 mm from which test samples were cut. The extruder used was Gimac micro extruder ϕ 12 mm L/D 24 and the zone temperatures were between 145–190 °C in the first extrusion and 140–180 °C in the second extrusion. In between the first and second extrusions, three months had elapsed during which time the polymer was stored in a dark desiccator in a closed container. A small batch of rods from the second extrusion were self-reinforced using solid-state die drawing at 100 °C [22]. Nitrogen was used as a protective gas in every processing stage. Specimens tested were not sterilized. Batch codes are listed in Table I.

2.3. Storage of samples

Prior to testing, devices were stored in small sealed double plastic bags, at room temperature in a desiccator and in the dark.

2.4. *In vitro* degradation

In vitro hydrolysis studies were performed at 37 °C in either PBS (pH 7.4 at RT) or SBF (pH 7.2 at 37 °C and pH 7.8 at 22 °C). Table II lists the experimental conditions. In all but one set of samples, buffer solutions were replaced fresh weekly. In all cases changes of buffer solution pH were determined.

2.5. Shear strength of the ultrasonically molded slabs

Shear strength of the ultrasonically molded slabs was determined by using a punching test. The method was modified from the standard method [23] by using smaller diameter devices and smaller diameter punching tool (6 mm). The testing was performed using an Instron 4411 materials testing machine (Instron, High Wycombe, UK) at a crosshead speed of 5 mm/min.

2.6. Shear strength of the rods

Shear strength testing of the rods was performed using an Instron 4411 mechanical testing apparatus at room temperature at a crosshead speed of 10 mm/min. Shear strength of the rods was determined with a tool modified [24] from standard [23].

2.7. Three-point bending strength and modulus of the rods

Bending strength and modulus of the rods were tested using an Instron 4411 mechanical testing apparatus at room temperature at a crosshead speed of 10 mm/min. Bending strength and modulus were determined using a three-point bending test according to standard [25], which calculations were modified to the cylindrical rods [24].

2.8. Thermal properties

Thermal properties of POE-LA samples were determined by Differential Scanning Calorimetry (DSC). For DSC measurements a Perkin Elmer DSC7 equipment (Perkin Elmer, Norwalk, CT, USA) was used. The DSC was calibrated with indium and experiments were performed under a nitrogen atmosphere. Results were calculated using baseline. Approximately 6 mg samples were heated from 27 °C to 215 °C and the heating rate used was 20 °C/min. The samples were then rapidly cooled and reheated using similar conditions. The glass transition temperature (T_g) was determined from baseline shifts and the cold crystallization temperature (T_c) and melting temperature (T_m), when observed, were determined at the maximums of the peaks.

2.9. Scanning electron microscopy (SEM)

Microstructure of samples was determined using a JEOL T100 SEM (JEOL Ltd, Tokyo, Japan). Specimens were prepared in liquid nitrogen in order to achieve a real fracture surface, followed by gold coating. Several different magnifications were used.

TABLE I Different specimen types marked with abbreviations used in the text

Processing	POE	POE + caffeine (2, 5 and 7 wt %)	POE + furosemide (2, 5 and 7 wt %)	POE-LA
Ultrasonic molding	USPOE	USPOECAF2, USPOECAF5, USPOECAF7	USPOEFUR2, USPOEFUR5, USPOEFUR7	USPOE-LA
Extrusion				EXPOE-LAI, EXPOE-LAII
Self-reinforcement				SRPOE-LA

TABLE II Hydrolytic treatments of different studied specimen sets

Specimen type	PBS	SBF
USPOE		X
USPOECAF ...		X
USPOEFUR ... [2]		X
USPOE-LA	X	X
EXPOE-LAI[2]	X	
EXPOE-LAII[2]	X[1]	

[1]One separate batch was *in vitro* in unchanged phosphate buffer solution for 20 weeks.
[2]Batches of these sets were stored in a dark desiccator to see the storability.

3. Results

3.1. Processing

Slabs were successfully fabricated by ultrasonic molding. All slabs were macroscopically excellent and all samples had even surfaces. In caffeine-containing samples the separate islands of drug were noted as already discussed in [16]. Furosemide containing samples had a yellow color indicating either decomposition of furosemide, or POE, or both.

Both extrusion experiments of POE-LA were successful. In the second extrusion, the melt pressure was lower despite lower zone and die temperatures and from that it was assumed that POE-LA had degraded while stored.

A piece of an extruded POE-LA rod was self-reinforced using solid-state drawing through a heated die. On the next day after extrusion, the drawing was successfully performed to the draw ratio 2.3.

3.2. Shear strength of ultrasonically molded devices

The shear strength values of all studied ultrasonically molded devices are shown in Fig. 2. The initial shear strength of USPOE, USPOECAF, USPOEFUR and USPOE-LA slabs varied between 46.1 MPa and 18.7 MPa depending on the polymer and the model drug used, and on the storage time. USPOE and USPOECAF samples yielded the highest strength values. Adding furosemide to the POE matrix remarkably weakened the structure and strength decreased from 42.8 MPa to 40.5–18.7 MPa depending on the quantity of furosemide used. In view of the known sensitivity of POEs to acid, this was clearly due to the acidicity of furosemide. Some USPOEFUR5 samples were stored in a dark desiccator for two weeks. The shear strength decreased from 42 MPa to 26 MPa. After the same storage time, the shear strength of USPOEFUR7 samples was 18.7 MPa.

It was of interest to note that the initial strength (20.8 MPa) of POE-LA devices resembled the strengths of stored USPOEFUR samples and there may be three possible reasons for this phenomenon:

1. The different chemical structures of the polymers.
2. The lactide segment incorporated into the POEs structure acidified the structure of the device as efficiently as the addition of 5–7 wt % of acidic drug furosemide did.
3. The POE-LA powder was processed six months post-delivery and it is possible that degradation took place during storage.

The hydrolysis of ultrasonically molded slabs was carried out for six weeks and the change of shear strengths is shown in Fig. 2. Three different behaviors were detected for slabs. USPOE and USPOECAF samples all showed similar type of strength loss. USPOEFUR2 and USPOE-LA (in PBS) have shown a similar behavior pattern that differed from the previous one and yet another behavior pattern was for USPOEFUR5, USPOEFUR7 and USPOE-LA (in SBF) slabs.

3.3. Mechanical properties of extruded and self-reinforced POE-LA rods

The initial shear strength of rods from the first extrusion was 41.2 ± 3.6 MPa and from the second extrusion 41.7 ± 1.7 MPa. These values were approximately similar to the strengths of USPOEFUR and USPOE-LA

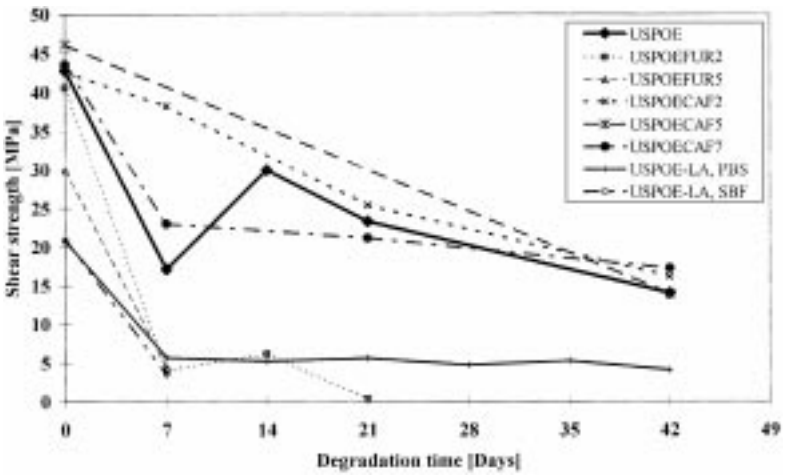


Figure 2 Shear strength values of ultrasonically-molded POE and POE-LA devices vs *in vitro* degradation time (SBF).

slabs. All the mechanical results of the rods showed high variations, and they were scattered, i.e. the strength did not decrease steadily vs time in hydrolysis in either case. This behavior is explained with non-homogeneous raw polymer which affected the samples.

The initial three-point bending strength and modulus of EXPOE-LA rods from first extrusion were 78.5 ± 22.8 MPa and 2.5 ± 0.3 GPa and from second extrusion 77.0 ± 13.2 MPa and 1.2 ± 0.2 GPa, respectively.

When EXPOE-LAII rod was drawn at a ratio of 2.3, mechanical properties increased remarkably to strengths of 66.7 ± 2.3 MPa (shear) and 182.7 ± 23.3 MPa (flexural) and to flexural modulus of 4.4 ± 0.3 GPa. Self-reinforcing was in agreement with our earlier studies of partially crystalline poly-α-hydroxy acids [22].

The results from storage tests are shown in Fig. 3. Three-point bending strength and modulus were higher for rods from the first extrusion than from the second one. No loss in shear strength or in three-point bending strength was observed during the maximum 168 days' storage time in either test. Three-point bending modulus of samples from first extrusion decreased while storing indicating the loss of stiffness. Neither dimensions, weight of rods or thermal properties changed during storage. However, an additional set of rods were stored in double plastic tubes with silica gel packets as drying agent. After four months of storage the rods turned very brittle and liquid was inside the inner plastic tube. The liquid was probably a degradation product of POE.

In hydrolytic conditions the rods from the first extrusion retained their mechanical properties longer than the rods from the second extrusion (Fig. 4). The shear strength remained approximately at the initial level 9 days with the samples from the first extrusion and 2 days with the samples from the second extrusion. Three-point bending strength decreased to 50% of the initial value during the first day and remained at that level for 3 days. The bending modulus of the first extrusion set rods (Fig. 5) was on average significantly higher than rods from second extrusion. The bending modulus decreased during *in vitro* periods. The rods were too fragile for further testing at indicated periods.

3.3. Thermal properties of POE-LA devices

Thermal properties of USPOE-LA samples are shown in Table III and T_g values are also shown in Fig. 5. Initially, USPOE-LA specimens were totally amorphous having a glass transition temperature 94 °C as determined from the first DSC scan. The T_gs were also determined from second DSC scans and in every case they were 3–12 °C lower than measured from the first scans. The heating and quenching runs altered the molecular structure of the studied sample causing lower T_g.

When hydrolyzed in PBS, USPOE-LA remained totally amorphous in the studied six-week period (Table III). When hydrolyzed in SBF, USPOE-LA or its degradation products started to crystallize at the first *in vitro* week. Both $T_{m\max}$ and H_m increased till 5 weeks indicating increasing size of crystals and a higher degree of crystallinity. In 6 weeks both features decreased drastically. The second DSC heating after rapid cooling (quenching) showed only T_g value for the samples.

Glass transition temperatures of POE-LA raw polymer and extruded rods were unchanged (102 °C). Changes of T_g after exposure to PBS are shown in Fig. 5. T_g remained at the initial level for the first week after which it rapidly dropped and then began to increase again after about one month *in vitro* exposure time. This was a similar kind of behavior as was found with ultrasonically molded samples.

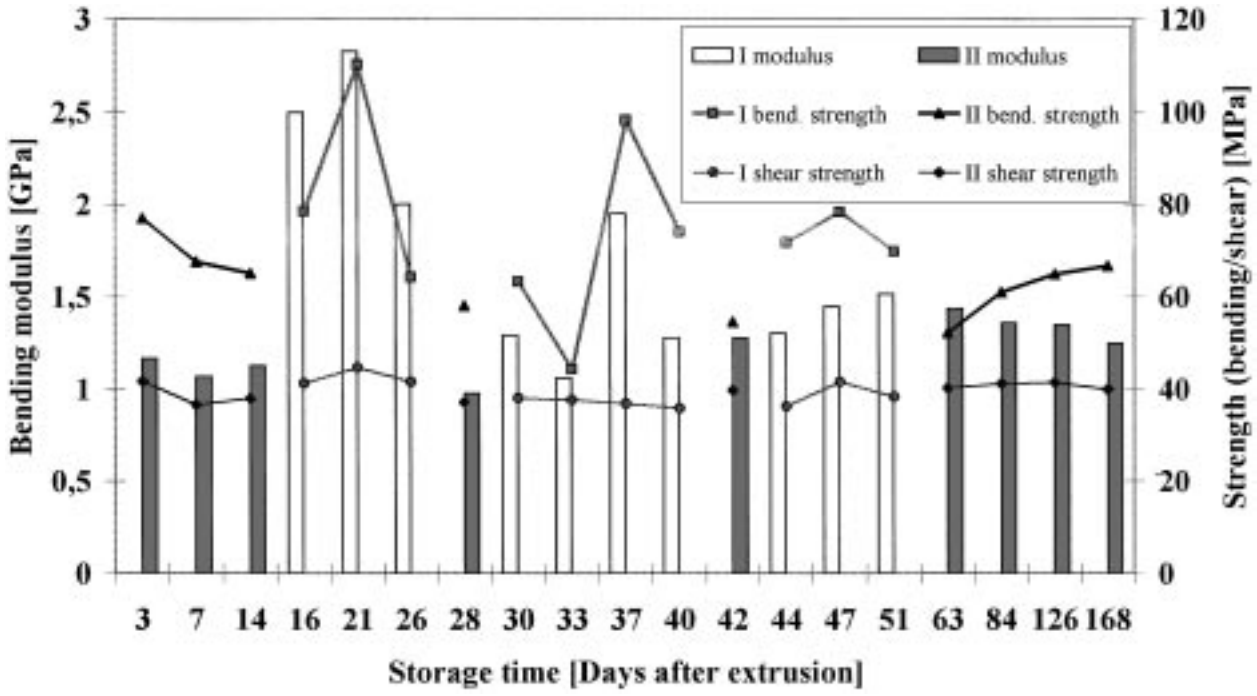


Figure 3 Shear strength, bending modulus and bending strength of stored EXPOE-LA rods vs storage time.

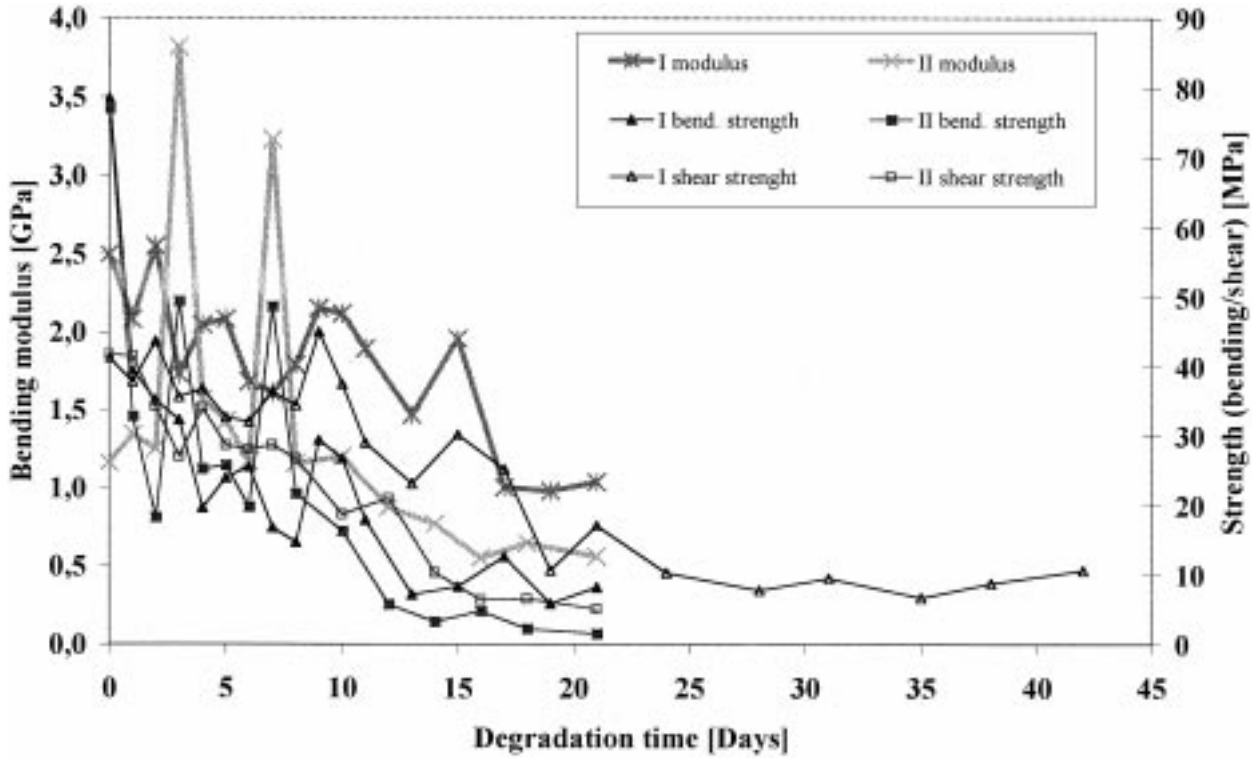


Figure 4 Shear strength, bending modulus and bending strength of hydrolyzed EXPOE-LA rods vs *in vitro* degradation time.

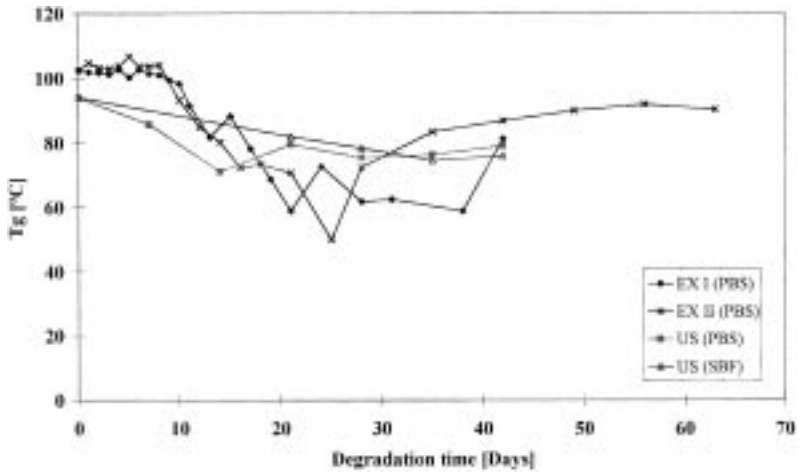


Figure 5 Glass transition temperature (T_g) of EXPOE-LA rods and USPOE-LA slabs vs degradation time.

TABLE III Thermal properties of USPOE-LA samples hydrolyzed in SBF and in PBS

Days	T_g (°C), 1. heating PBS	T_g (°C), 2. heating PBS	T_g (°C), 1. heating SBF	T_c (°C) / H_c (J_g^{-1}), 1. heating SBF	T_m (°C) //H_m (J_g^{-1}), 1. heating SBF	T_g (°C), 2. heating SBF
0	94.1	81.0	94.1	–	–	81.0
7	85.8	76.5	–	87.3/ – 1.65	131.9/4.93	49.8
14	71.1	68.8	–	–	140.6/16.21	46.6
21	79.4	69.5	82.0	–	–	74.4
28	75.3	69.5	78.3	–	139.0/4.91	59.9
35	76.3	70.3	74.5	99.9/ – 0.92	151.9/55.71	–
42	79.2	72.1	75.9	–	136.9/2.58	62.1

3.4. Physical changes of EXPOE-LAII rods *in vitro*

In Fig. 6 weight and diameter changes of extruded POE-LAII rods and pH of the buffer solutions are shown in per cent. The pH of unchanged PBS decreased, while the pH of changed PBS practically remained constant during the whole study period. As expected, the pH decrease enhanced the degradation of POE-LA matrix seen from the weight loss rate and diameter (dry) changes. The wet and dry diameter of both sample types diminished for certain time periods after which dry diameter decreased faster in both cases.

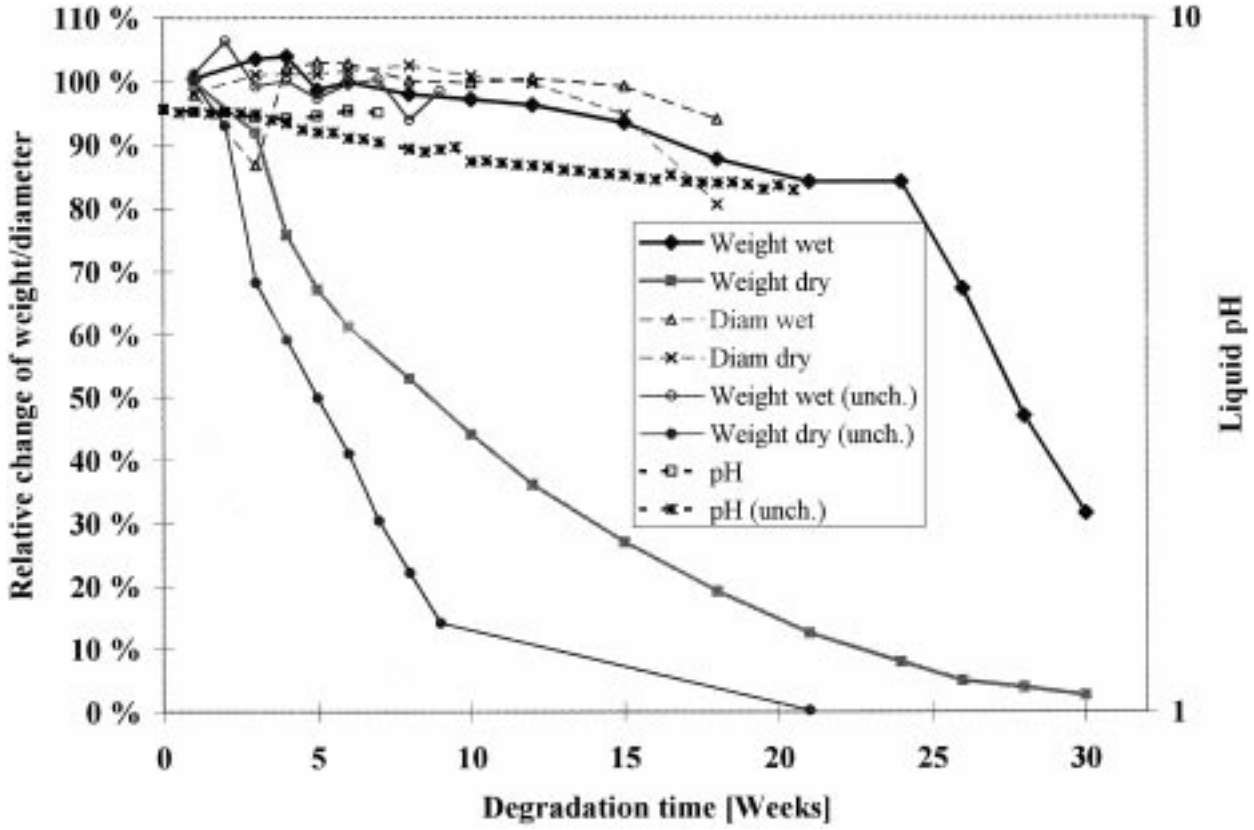


Figure 6 Weight and diameter of EXPOE-LAII rods relative to initial values vs degradation time, and the change of pH of changed and unchanged PBS vs degradation time.

3.5. Structural studies of POE and POE-LA samples

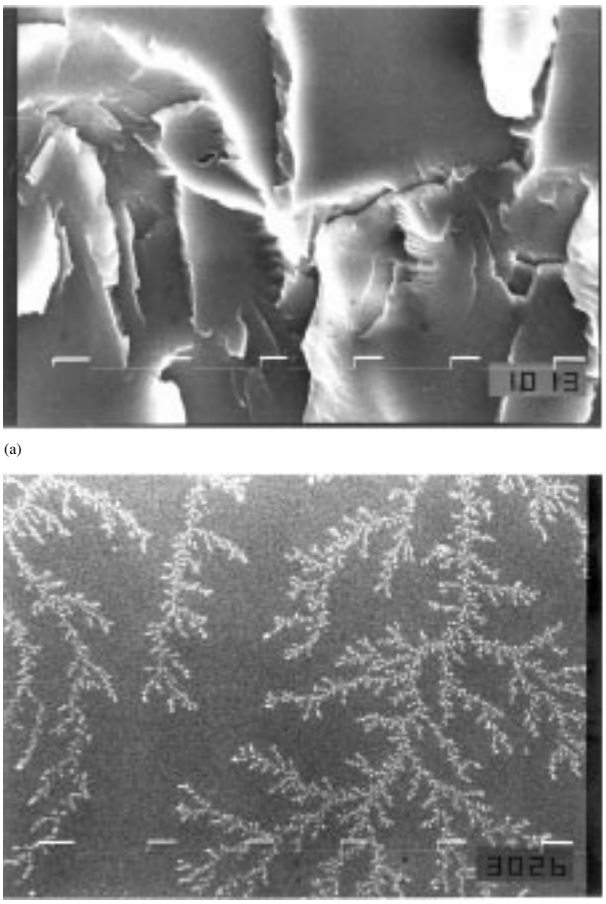
3.5.1. Ultrasonically molded samples

The plain USPOE and USPOE-LA samples had a nicely formed surface with no clearly visible powder particle boundaries (as reported earlier in [16]). On a fracture surface, however, the particle boundaries could be seen (Fig. 7a). The samples had therefore not become dense throughout and uniform in processing.

When the USPOE samples were hydrolyzed in SBF, the surface of the samples underwent different stages of porosity and craking, indicating surface erosion during the study period. The erosion seemed to start at former particle boundaries. No crystalline structures were seen on the surfaces of the samples. On the fracture surfaces of USPOE samples no clear degradation or erosion signs were noticed. However, during the first hydrolysis week, signs of emerging crystal formation could be seen. In the six-week samples (Fig. 7b) the crystalline, branched structures had grown to a network. This structure could have been crystallized and/or partially degraded polymer or crystallized monomer.

The hydrolysis of the USPOE matrix caused by acidic drug furosemide was clearly seen in SEM studies and thus confirmed the strength results. Matrix polymer dissolved due to the added drug and later the eroded spots were seen on the surface of the slabs.

In the USPOECAF samples physical appearance of caffeine had turned on the surfaces of the samples to needle-like during processing while it remained more original inside the ultrasonically molded specimens (Fig. 8a and b). At the studied six-week period, caffeine did



(a)

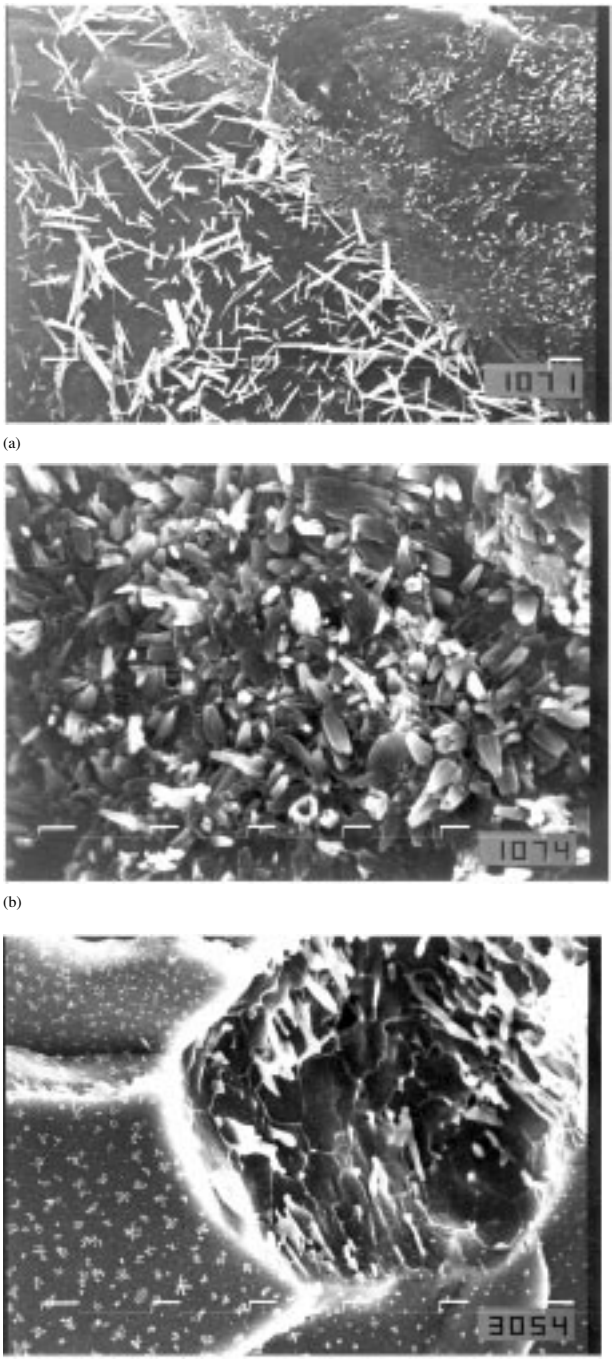
(b)

Figure 7 Scale bar length (between the tick marks) in both photos 10 μm. (a) A fracture surface of USPOE sample. (b) A fracture surface of USPOE sample after six weeks *in vitro*.

not degrade the matrix as furosemide did. Caffeine gradually disappeared from the fracture surfaces and the insides of the USPOECAF sample matrix remained more intact with only small signs of degradation over the studied period. Already after the first week the crystalline structures growing inside the polymer matrix were visible. The branches were similar to the ones seen in USPOE sample (in Fig. 7b). Only USPOECAF7 samples showed no crystal formation in the matrix before 6 weeks follow-up time. In that, a small-scale crystal formation is seen in polymer matrix (Fig. 8c). The crystals are very small, 1–1.5 μm (when measured from a higher magnification photograph which is not presented here).

USPOE-LA samples degraded much faster in SBF than USPOE samples. After the first week in SBF the sample had degraded to a greater extent than USPOE had degraded in six weeks. Surface erosion was not noted and these samples at weeks 2–6 had broken into pieces that gradually eroded smaller. The surface structure of these pieces became smoother and the holes became more numerous and finer when hydrolysis time extended (Fig. 9a) showing the occurring erosion. No crystalline structures were seen in these samples.

The degradation of USPOE-LA samples hydrolyzed in PBS was slower than in SBF. The erosion was obvious when sample surface and fracture surface near sample surface and inside the sample were studied versus time in

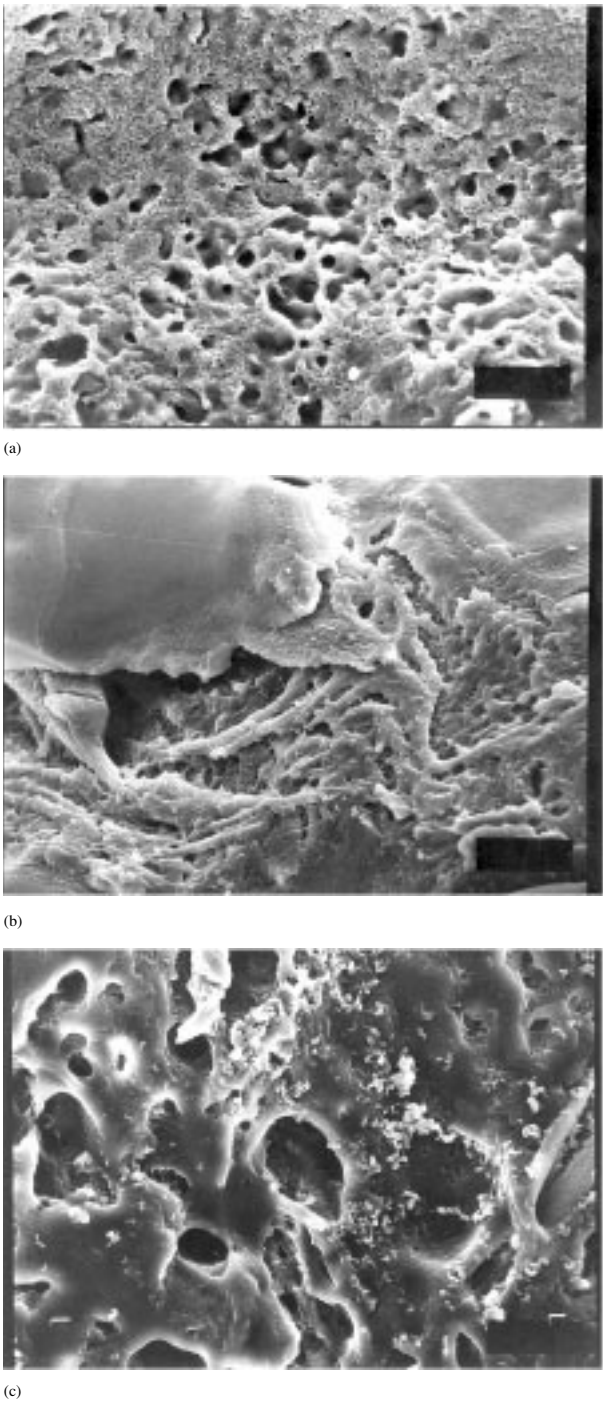


(a)

(b)

(c)

Figure 8 Scale bar length (between the tick marks) in all photos 10 μm. (a) A surface of USPOECAF7 sample. (b) A fracture surface of USPOECAF7 sample. (c) A fracture surface of USPOECAF7 sample after 6 weeks *in vitro*.



(a)

(b)

(c)

Figure 9 Scale bar length (between the tick marks) in all photos 100 μm. (a) A structure of USPOE-LA sample after 6 weeks *in vitro* (SBF). (b) A fracture surface close to surface of USPOE-LA sample after two weeks *in vitro* (PBS). (c) A fracture surface inside the USPOE-LA sample after six weeks *in vitro* (PBS).

PBS. The surface of the sample underwent rough and smooth stages depending on the hydrolysis time. The erosion front is seen on fracture surfaces of the specimens. For example, after two weeks in PBS, the structure of the sample close to the surface had already begun to erode with pinholes etc. (Fig. 9b). Also, the structure inside the sample had changed with deeper grooves that were probably grown onto the boundaries of original powder particles but otherwise the polymer seemed intact. The resorption grew from the surface towards the inner part of the sample and finally the structure was somewhat similar throughout the sample to that of Fig. 9c which is an example from the sixth week *in vitro*.

3.5.2. Extruded samples

Extrusion made the sample structure denser than ultrasonic molding with chosen processing parameters. In both changed and unchanged solution cases the samples underwent a faster degradation closer to surface than in inner parts of the rod, as can be seen from Fig. 10a, where the porous outer layer is above and the denser inner layer is below. In the unchanged solvent case (Fig. 10b) the changes of the structure became visible earlier than in changed buffer solution (Fig. 10c). Also, the change of the diameter of rod is seen as the initial diameters were equal. Samples hydrolyzed 30 weeks in periodically changed PBS solutions showed degradation of the same extent with unchanged PBS solution samples at 10 weeks.

Probably due to a denser structure in the beginning, no such clear and rough surface erosion is seen with extruded rods as is seen in ultrasonically molded samples until the degradation is present through the rod.

4. Discussion

The studied POE and POE-LA degraded while stored, sealed over drying agent at ambient temperature, as has also been the case in [20, 26]. The storage degradation is seen when *in vitro* strength retention of two extruded sets is compared (Fig. 4). Most probably the molecular weight changes had indicated the degradation of both raw polymers and melt-processed samples, but unfortunately those measurements could not be performed at the time. Due to continuous degradation, the measurements were not relevant afterwards.

In this work, the two studied POEs were found to be relatively easily processed with the chosen two methods and no big differences were found when compared to the processing of well-known bioabsorbable polymers, like polylactides. Principally, both initial strengths and initial bending modulus were comparable to the results previously reported either for non-reinforced POEs [10, 19, 27] or, for example, polylactides [22]. The shear strengths were also approximately similar when these two processing methods were compared to each other. However, the processing methods gave different structures for the POE-LA samples. This was seen from different glass transition temperatures but also in SEM studies. Ultrasonic molding left the structure softer and also less dense with slight porosity compared to extrusion that gave an initially dense structure to the sample.

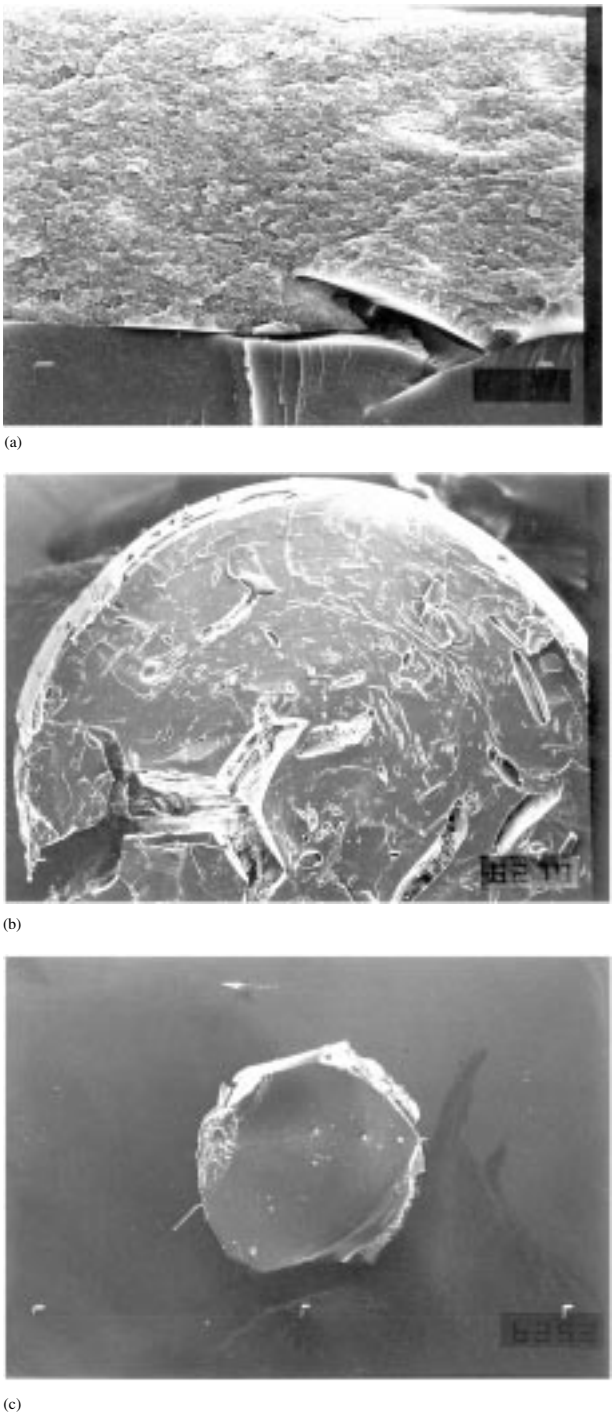


Figure 10 In (a) scale bar length (between the tick marks) 100 μm. In (b) and (c) the scale bar length (between the tick marks) 1000 μm. (a) A fracture surface of EXPOE-LAII sample after six weeks *in vitro* (PBS, changed solution). (b) A fracture surface of EXPOE-LAII sample after twelve weeks *in vitro* (PBS, changed solution). (c) A fracture surface of EXPOE-LAII sample after ten weeks *in vitro* (PBS, unchanged).

The *in vitro* strength retention time was shorter for these POEs than in [5, 10, 27]. POE, however, had a different kind of chemical structure compared to earlier ones. Blending the furosemide enhanced the degradation rate as the drug was acidic. Furosemide addition made POE behave somewhat similarly with studied POE-LA both in storage and *in vitro*. Addition of caffeine had only a minor effect on the degradation of POE and therefore in this case the boundaries between the matrix polymer

(POE) and the filler (caffeine) did not enhance the solution diffusion into the specimen structure.

The strength retention time of POE-LA was expectedly shorter than in similar types of POE without lactide due to the acidic lactide copolymerized into its structure [5, 10, 27]. Also, the initial bending strength was lower than previously reported [10, 19, 27]. The self-catalyzed degradation had probably started immediately after processing because drawing experiments were successful right after processing, but not later on. The bending strength started to decrease *in vitro* faster than the shear strength.

Rods from the first extruded set retained their strength longer *in vitro* than rods from the second set. This is probably due to stored and thus degraded raw polymer. The reason why the strength retention behavior of ultrasonically molded slabs was in between the behavior of rod sets is probably in processing. The structure of the rods is denser making water diffusion into the structure slower. On the other hand, extrusion is a more stressing processing method and thus affects sensitive materials more than ultrasonic molding.

Previously, some more hydrolysis studies using solutions with different pH (1.0–7.4) have been reported [15, 28, 29]. Not only the pH of the solution but also the hydrophobicity/hydrophilicity of the solution has been found to effect the degradation of POE. Hydrophilic solutions enhance the degradation rate [28].

It was seen from results that the lower the pH of PBS the faster the degradation. The PBS solution turned acidic when unchanged and the degradation of the POE-LA was enhanced compared to the set of samples in changed solution. The degradation rate judged from the SEM photos was similar for the 10 week sample from unchanged solution compared to the 30 week sample from changed solution.

As two different buffer solutions were used, these studies showed that not only the pH of the solution but also the ionic consistence is critical for the POEs degradation. SBF gave much harsher treatment to POE-LA devices than PBS. The strength of the slabs hydrolyzed in SBF decreased much earlier (after the first *in vitro* week). After 6 weeks *in vitro* in PBS USPOE-LA devices still had remaining strength while only small crumbles were left of the similar devices hydrolyzed in SBF.

The difference between PBS and SBF as hydrolysis solutions was also seen in thermal properties or in microstructure studied by SEM. SBF hydrolyzed USPOE-LA samples started to show melting endotherms (i.e. crystallinity) already after the first week *in vitro*. Samples subjected to PBS retained their amorphous structure through all six weeks as determined from the DSC scans. The SBF made both POE and POE-LA form crystals *in vitro* visible in SEM micrographs. Whether the crystals were monomers, oligomers or polymers remains an unsolved question. The crystallization of POEs or their degradation products has not been reported earlier.

Detailed thermal behavior results have been reported for POEs when the effect of used diols to polymer structure have been studied [14, 30–32]. It was reported that when the initial glass transition temperature is lower the degradation is faster [33]. No clear influence was seen in these results as the chemical structures were so different and had stronger influence on behavior than glass transition temperature.

POE-LA remained amorphous during the studied two processing procedures but the glass transition temperature was remarkably lower for ultrasonically molded samples than for extruded samples. The differences in glass transition temperatures indicate that these processing methods allow different kinds of amorphous structures to form in the samples. In ultrasonic molding the heating and cooling stages of processing are so rapid, heating only parts of second and cooling only some seconds, that the polymer has no time to arrange, not even to an ordinary amorphous state. In extrusion the heating and cooling stages last longer and give more time for the structure to form and arrange to that extent which is possible to occur with an amorphous polymer. A similar kind of behavior has been reported in [16] for poly-L-lactide but in that case melting temperature was studied as the polymer was originally partially crystalline.

This structural difference of either ultrasonically molded or extruded samples made the samples behave differently when hydrolyzed. Ultrasonically molded slabs eroded from the surface more clearly than the extruded rods except that the copolymerized lactide in the POE-LAs structure made it erode too fast for our follow-up times. Extruded rods also eroded from the surface but not as clearly. After a certain point, when the diameter of the rods started to decrease when dried, we were not able to say according to our studies whether the degradation spread throughout the structure due to the collapsed structure.

5. Conclusions

Both ultrasonically molded and extruded samples of both types of POEs showed initial mechanical strength values typical for non-reinforced biodegradable polymers. The extruded POE-LA rods could be drawn to create a self-reinforced structure for this totally amorphous polymer.

The hydrolysis rate of the studied POEs, as measured by strength loss of the polymers, was too rapid for load-bearing orthopaedic applications. The rate was clearly affected by the selection of additives, in this case either by drug or by copolymerized lactid acid.

The degradation of POE when stored was very alerting as it also happened in an unpredictable manner. Therefore either the raw polymer or processed POE or both must be developed further to make it less inclined to storage degradation.

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