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Research paper

Injection-molding versus extrusion as manufacturing technique for the preparation of biodegradable implants

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Abstract

Polylactic acid (PLA) is a biocompatible and biodegradable material with wide utility for many applications, including the design of controlled-release systems for pharmaceutical agents. The factors determining the degradation kinetics of these systems include the composition and the molecular mass of the polymer, the morphology and the structure of the device, and the influence of thermal processes. The processing of the polymer determines the structure and design of the device, and influences to a high degree its morphology, namely its microporous structure, polymeric chain orientation and crystallinity.

In this work, we aimed to compare the influence of two different implant manufacturing techniques, extrusion and injection-molding, on the in vitro degradation of the polymeric matrix. Both kinds of implants were loaded with a somatostatin analogue. Decrease in molecular weight, and polydispersity evolution during an accelerated in vitro degradation test were studied by size exclusion chromatography. Morphological changes in the polymeric matrix during degradation were followed after defined time intervals by means of scanning electron microscopy. Crystallinity studies were performed by differential scanning calorimetry and by X-ray analysis. Peptide stability in the polymeric matrix after both manufacturing methods was evaluated. Peptide release profiles, obtained in vitro during a week dissolution test, from both implant samples, were studied.

It was shown that both molecular weight and polydispersity decreased after extrusion or injection-molding. This decrease was more pronounced with the latter technique. Crystallinity studies demonstrated that the crystalline network was not destroyed after both manufacturing methods. Peptide release profiles obtained in vitro were in good accordance with scanning electron microscopy. It was found that both manufacturing techniques had to be considered, although the extruded implants degraded more rapidly in vitro than the injection-molded ones.

Keywords: Somatostatin analogue; Polylactic acid; Implant; Injection-molding; Extrusion; Controlled release

1. Introduction

Biodegradable and bioresorbable polymers, since they degrade after application into products that are eliminated from the body by excretion or respiration, have attracted the interest of various research groups. One of the important applications of bioresorbable polymers is the development of controlled release products for parenteral applications, such as implants or microparticulate systems [1–3]. A variety of polymers has been used for such applications [4]. The most widely investigated polymers in regard to available toxicological and clinical data are the aliphatic polyesters based on lactic acid (PLA), glycolic acid (PGA), and their copolymers (PLGA) [5,6]. Their long clinical use as surgical sutures demonstrates that they are biocompatible in physiological environments as they are hydrolyzed into metabolic by-products that are eliminated from the body [7]. Transport of drug from depot systems based on these polyesters is of a rather complex nature. The degradation properties of the polymers, the manufacturing technology as well as the relative drug loading of the device determine the in vivo performance of the delivery system [8–12]. Indeed, it can be appreciated that polymer implants produced by

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melt extrusion or injection-molding, owing to the different manufacturing processes, may not have the same final molecular weights, crystallinity or microporous structures, and will therefore degrade at different rates [13]. The properties of extruded or injection-molded products, such as polymer chain orientation and crystalline/amorphous ratio, will depend on the conditions of the molding operation as well as any thermal treatments used after molding [14]. Depending on the manufacturing process employed, macro- or microscopic differences in the final products will appear. Thus, each final implant will have to be individually evaluated in vitro.

Thermoplastic polymers, which include PLA and PGA, soften and melt on heating and can potentially be shaped in a variety of implants using several techniques, such as injection-molding, compression-molding, and extrusion [14]. However, the limited stability of commercially available biodegradable polymers at high temperatures and especially under shearing forces, is a main concern when using melt-processing. Another limiting factor, in regard to melt processing of implants for drug delivery, is the heat stability of the active agent, e.g. peptides [15], since most of the lactide/glycolide polymers are injection-molded or extruded at temperatures between 80 and 175°C [16].

So far, there have been few reports on the influence of the manufacturing method on implants, and their characteristics have not received much attention.

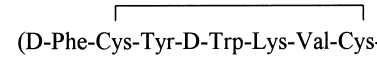
Our goal was to develop biodegradable implants suitable for the prolonged release of vapreotide, a somatostatin analogue, by two different manufacturing methods, injection-molding versus extrusion. The present study aims at comparing the properties of both kinds of implants. Strength forces measurements allowed the comparison of the implant behavior to stresses. The in vitro degradation behavior of both types of implants was studied. Investigations dealing with changes of molecular weights and polydispersity, were followed by size exclusion chromatography (SEC). The implants were also characterized by scanning electron microscopy (SEM), during the in vitro degradation test. Crystallinity was followed by differential scanning calorimetry DSC and by X-ray analysis. The polymeric structure of the implants was further investigated by infrared (IR) spectroscopy. The in vitro peptide release profiles obtained from both kinds of implants were investigated, as well as peptide purity after both manufacturing methods. The advantages and disadvantages of both manufacturing methods are then discussed.

2. Materials and methods

2.1. Materials

The poly(L-lactic acid) L 104 (100 P(L)LA, Mw 6000) was purchased from Boehringer Ingelheim (Ingelheim am Rhein, Germany).

The somatostatin analogue vapreotide in the form of the pamoate derivative was obtained from Novabiochem (Basel, Switzerland).



All other chemicals were of analytical grade and used without further purification.

2.2. Methods

2.2.1. Implants preparation

For the extrusion technique, implants were obtained by extruding mixtures of L 104 and vapreotide pamoate at a core loading of 18.5% (vapreotide, calculated as base) with a laboratory ram extruder as described previously [17]. The powder was introduced in a barrel of 10 mm inside diameter, in which a piston rod (10 mm in diameter) was inserted and then moved into the barrel under an appropriate pressure. The extrusion temperature was 80°C. The die had a diameter of 4.6 mm, and the rods were cut into implants of 2.75 cm length.

For the injection molding technique, a special adapted injection molding machine (Babyplast, Chronoplast, Barcelone, Spain) was used. The mold used had a diameter of 4.6 mm and a length of 2.8 mm. One of the implant ends was round shaped, in order to facilitate a possible implantation under the skin. The plastification temperature was 110°C, the injection temperature was 100°C, and the cooling was at a temperature of 14°C. The injection pressure was set at 130 bars.

2.2.2. In vitro studies

In vitro studies were performed on whole implants, using the paddle method (USP XXIII apparatus 2) at 200 rev./min, in 500 ml medium. The release medium, maintained at 37°C, was a mixture of methanol and water (50:50). It was not replaced over the whole testing period. At defined time intervals, dissolution medium samples were collected for peptide content analysis, and implant samples were collected for SEM and SEC testing. The release medium was chosen to allow complete release of the incorporated drug in the implants within 2 weeks. This 'accelerated' test is not predictive for in vivo performance, but allows a comparison between manufacturing methods.

2.2.3. Analytical methods

Vapreotide content and impurity levels were determined using a gradient reverse-phase HPLC assay with detection at 220 nm (Waters 600 controller, multisolvent delivery system equipped with a UV detector, detector Waters 486, tunable absorbance detector, Rupperswil, Switzerland), and an automatic injector (Waters 700 satellite WISP, Rupperswil, Switzerland). The Millenium 2010® chromatography manager was used to analyze the data (version 2.1). The mobile phase consisted of a mixture of phosphoric acid–

triethylamine pH 2.3 solution buffer and acetonitrile. The flow rate was 0.8 ml/min. The vapreotide peak area was compared to the peak areas of the total number of peaks and was expressed as a percentage (the areas of the pamoic acid peak and the peak system were not included).

2.2.4. Size exclusion chromatography (SEC)

After defined time intervals, implant samples were removed from the dissolution medium and freeze-dried, before analysis. Weight average molecular weight measurements were performed on a Waters 150C high-pressure SEC equipped with three series mounted Styragel columns, respectively a HR 1 column (with an effective molecular-weight range from 100 to 5000, Waters), a HR 2 column (500–20 000, Waters) and HR 4 column (5000–500 000, Waters). Chloroform was used as the mobile phase; the injected sample volume was 200 μl, the sample concentration was 0.1 wt.%, the temperature of columns was 30°C, the flow rate was 1.0 ml/min. Injections were performed using a Waters 717 autosampler.

To calibrate the system, monodisperse polystyrene standards of the following molecular weights were used: 5.0×10^2, 2.63×10^3, 5.97×10^3, 9.1×10^3, 1.81×10^4, 3.79×10^4, 9.64×10^4, and 3.55×10^5 daltons (Tosoh Corporation, Japan).

2.2.5. Scanning electron microscopy (SEM) and strength forces measurements

After defined time intervals, implant samples were removed from the degradation medium and dried under vacuum, before characterization by SEM. Scanning electron micrographs were performed by means of the JSM-6400 scanning microscope (JEOL LTD, Japan).

The strength forces measurements were performed using an adapted force tester (Schenk-Trebel RM 50, CH-Nänikon), fitted with force and displacement transducters (Type U1 and Type W5TK, Hottinger–Baldwin Messtechnik HBM, D-Darmstadt) and driven by a control unit.

2.2.6. Crystallinity and infrared spectroscopy (IR) studies

The crystallinity of P(L)LA was evaluated qualitatively by means of differential scanning calorimetry. DSC thermograms were obtained using a differential scanning calorimeter (Perkin–Elmer, DSC-4), with a heating rate of 10°C/min. The crystallinity of the P(L)LA rods was also examined using powder X-ray diffraction. Powder X-ray diffraction patterns were obtained from a Guinier camera (Cu, $K\alpha_1$, 1.54056 Å, Enraf Nonius, Delft, Holland).

The different implant samples were ground into powder and analyzed by IR spectrometry (Perkin Elmer® AG Model 1600, FT-IR spectrometer, Küsnacht, Switzerland) using KBr tablets.

3. Results and discussion

3.1. Macroscopical implant aspects

Immediately after manufacturing, implants produced from injection-molding and extrusion were compared. Macroscopically, all samples were smooth and similar in appearance. However, the visual inspection of the implants showed a better color uniformity (due to vapreotide pamoate which had a yellow color), in the injection-molded samples (Fig. 1).

The implant diameters were little different, although the die of the extruder had the same diameter than the mold of

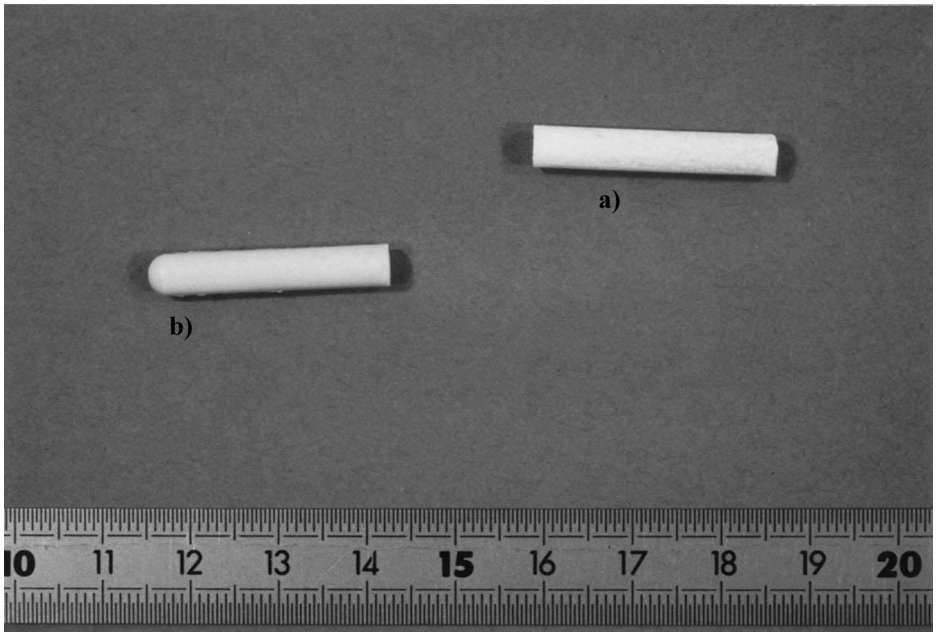


Fig. 1. Macroscopical aspect of extruded (a) and injection-molded implants (b).

Table 1
Forces applied until the breakage of the implants occur.

Production method	Forces applied (N)	
	Longitudinally	Perpendicularly
Injection–molding	76.99 ± 22.58	36.72 ± 14.77
Extrusion	72.93 ± 19.01	32.22 ± 9.41

the injection-molder. The extruded implants showed a diameter of 4.75 mm, whereas the injection-molded ones showed exactly the diameter of the mold, i.e. 4.6 mm. However, the weight of both implant samples was the same (550±22 mg), suggesting a higher matrix density for the injection-molded implants.

Both implant samples exhibited somewhat brittle characteristics. The strength forces needed for braking the implants longitudinally and perpendicularly to the longitudinal axis were measured.

It can be seen from Table 1, that both kinds of implants are more resistant to the break longitudinally than perpendicularly. This can be explained by the polymer chain orientation, which occurs during the manufacturing process. All samples had to be carefully handled, although the injection-molded implants showed mean forces a slightly higher than those seen with the extruded ones.

3.2. Analysis of weight average molecular weight and polydispersity during in vitro degradation

Among other factors, such as crystallinity, glass transition temperature or water uptake, weight average molecular weight (Mw) and number average molecular weight (Mn) determine the rate of degradation of polylactic implants, with the rate being slower for high molecular weight materials [4,18,19]. Generally, a decrease in polymer Mw and Mn is observed after a melt manufacturing technique [12,20,21]. We observed this phenomenon after extrusion and injection-molding: the Mw of the raw material was 9096 daltons, whereas implants obtained after both manufacturing methods showed a Mw below 6000 daltons (Mn data are not shown). Moreover, right after manufacturing, both implant samples showed a smaller Mw than after 1 h immersion in the degradation bath. This phenomenon can be explain by the fast solubilization of oligomers due to the high percentage of methanol (measured values corresponded to solid samples and did not account for soluble oligomers released from the samples). The raw material showed a narrow and unimodal molecular weight distribution, whereas both implant samples showed broadened and bimodal molecular weight distributions (not shown).

It has been reported that semicrystalline P(L)LA develops a multimodal weight distribution upon degradation [22]. This is due to a preferential degradation of the amorphous domain. Therefore, it was concluded that the bimodal

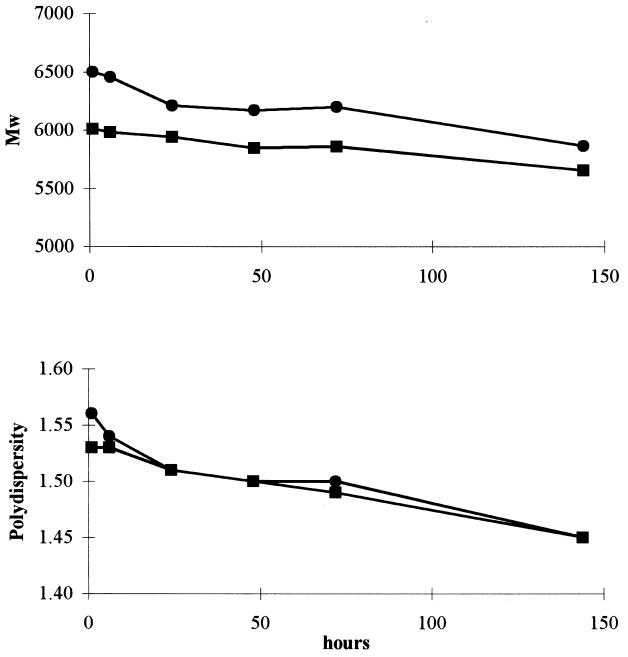


Fig. 2. Mw and polydispersity decrease during an in vitro dissolution test. (-■-) injection-molded implants, (-●-) extruded implants.

weight distribution in our results was attributable to such heterogeneous degradation of the semi-crystalline P(L)LA.

The overall aspect of the SEC curves changed little during the degradation test, since L-PLA low molecular weight chains may be hydrolyzed into units showing similar elution rates, or into soluble oligomers [23]. This phenomenon may explain the little decrease in Mw observed during the accelerated in vitro degradation test over 1 week (Fig. 2). Compared to a degradation test carried out in water, the addition of methanol improves polymer solvatation and increases degradation rate.

It can be seen from Fig. 2, that for both samples, there is a tendency for Mw and polydispersity to decrease during the overall degradation test. Mw and polydispersity profiles are almost the same for both samples, although the injection-molded implants showed from beginning to end a smaller Mw than the extruded ones. During injection-molding, the polymer is exposed to temperatures higher than 100°C, to high pressures of up to 1000 bars, and to great shearing forces [24]. In contrast, during the extrusion process, the matrix is exposed to temperatures below 100°C and to pressures of up to 100 bars. These differences may explain the higher Mw decrease after manufacturing, in the injection-molded implants.

Mw decrease appeared to be independent of the Mw at the beginning of the degradation test. It was reported [14], that an exponential increased degradation occurs only once the molecular weight of L-PLA decreases below 5000 daltons.

3.3. Crystallinity studies of the P(L)LA implant matrices

Crystallinity can be described as an arrangement of mole-

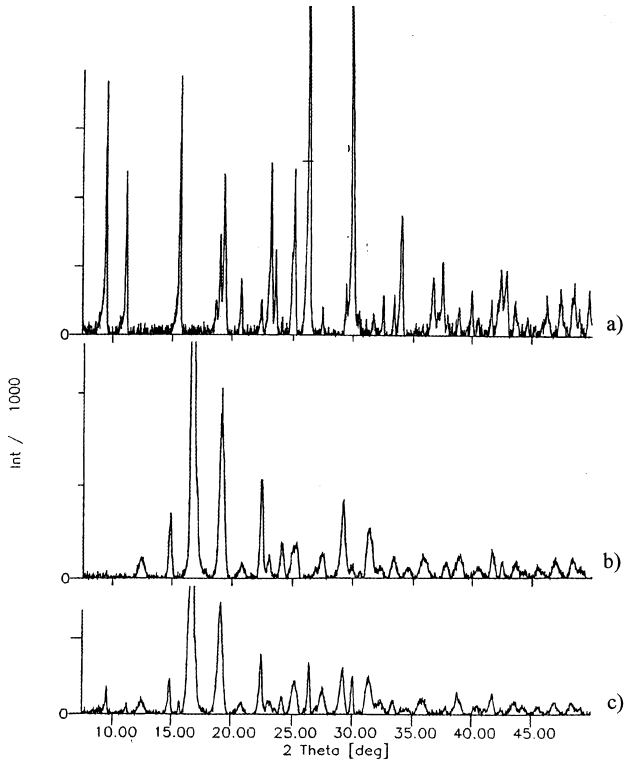


Fig. 3. X-ray diffraction patterns of pamoic acid (a), P(L)LA (b) and injection-molded implants containing pamoic acid (c).

cular chains that results in an ordered structure. Most polymers display little crystallinity and are either amorphous or semicrystalline. Semicrystalline polymers, such as L-PLA, contain crystalline regions as well as disordered amorphous regions. Because ester groups in crystalline regions are resistant to hydrolysis, the rate of chain cleavage should increase with decreasing degree of crystallinity. Parameters that influence the crystallinity of a polymer are those that provide polymeric molecular chains to reorganize themselves into a more-ordered, and thereby lower, energy state. Elevated temperatures and a slow rate of cooling enable the chains to be mobile and to realign themselves in a more-ordered solid structure [13,22]. Thus, crystallinity of PLA polymers can be altered as a result of melt manufacturing techniques for which heat is used, as well as the degree of crystallinity can depend upon the rate of cooling during solidification from the melt.

We evaluated the crystallinity of both kinds of P(L)LA rods with a DSC and powder X-ray analysis. The DSC thermograms of pure P(L)LA and of both kinds of implants showed endothermal P(L)LA peaks at 130–140°C (not shown). All the thermograms were similar. The surface area under the curve, which could be assigned to the degree of polymer crystallinity, were not significantly different.

The powder X-ray diffraction patterns of P(L)LA, pamoic acid, and injection-molded implants containing pamoic acid are shown in Fig. 3.

It is evident that the P(L)LA before extrusion or injection-molding has crystalline regions because there are significant sharp diffraction peaks. Pamoic acid is also crystalline, whereas vapreotide (not shown) is completely amorphous. The powder X-ray diffraction pattern of the extruded implants containing vapreotide (not shown) showed no difference with that of P(L)LA. On the other hand, the pattern of the injection-molded implants containing pamoic acid showed the exact superposition of both P(L)LA and pamoic acid patterns. These results indicate that the low molecular weight drug incorporated in the P(L)LA polymeric matrix during a melt manufacturing method, does not interfere with the crystalline network and may be dispersed in the amorphous phase of the polymer or at its surface. In addition, it can be concluded that none of the melt-manufacturing techniques had altered the crystalline network of the polymer.

However, nor the DSC, nor the powder X-ray analysis technique used can detect a slight increase in the percentage of crystallinity in the polymeric matrix. As only a slight increase in crystallinity may influence largely the matrix degradation, different drug release profiles from both kinds of implants may be observed.

3.4. IR spectroscopy studies of the P(L)LA implant matrices

From Fig. 4, it can be appreciated that the extruded (d)

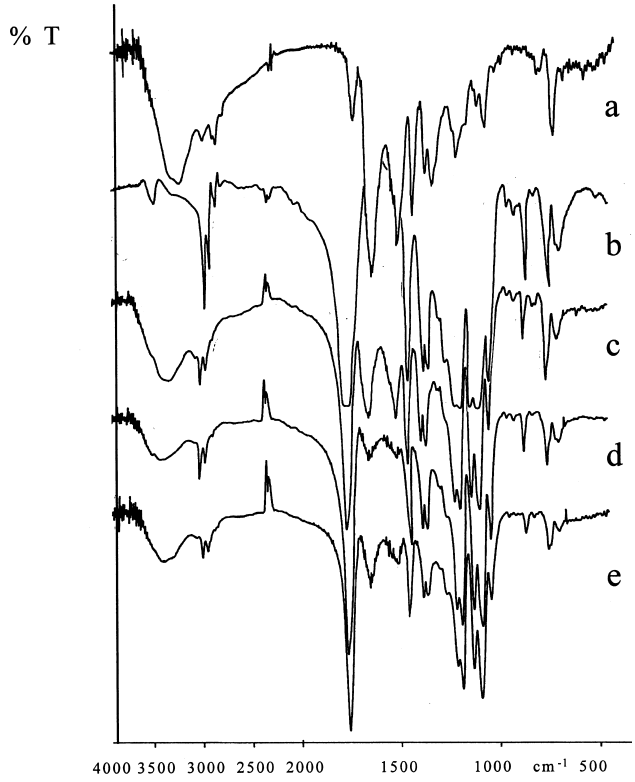


Fig. 4. FTIR spectra of vapreotide (a), P(L)LA (b), physical mixture of vapreotide and P(L)LA (c), extruded P(L)LA implant containing vapreotide (d) and injection-molded P(L)LA implant containing vapreotide (e).

and injection-molded (e) implant spectra show the superposition of both vapreotide (a) and P(L)LA (b) spectra. These results confirm the X-rays studies, where it was shown that no chemical reactions occurred between the peptide and the polymer during any of the melt manufacturing processes. In addition, it can be observed that there are some differences between the extruded and the injection-molded spectra. Indeed, for the injection-molded P(L)LA spectrum, the relative intensity of the characteristic ester band ν (C=O) at 1750 cm^{-1}, in comparison with the intensity of the hydroxyl groups band $\nu_{s,as}$ (O—H) at 3300 cm^{-1}, is less intense than for the extruded P(L)LA. As seen by SEC, this result can be explained by the increased polymer degradation in the injection-molded implants as compared to the extruded ones, immediately after manufacturing.

3.5. Implant degradation characterization by scanning electron microscopy

Water uptake has been proposed as a tool for regulating degradation rates of polymers. It was suggested that absorption of water is accompanied by ester bond cleavage and molecular weight decrease [25–27]. Degradation of L-PLA in the aqueous media proceeds via a random, bulk hydrolysis of ester bonds in the polymer chain, with a rate dependent on the polymer crystallinity [23,28]. The degradation rate of a particular sustained release delivery system will change with time, depending on the polymer decomposition within the matrix.

An implant obtained from each manufacturing method was degraded in vitro. The rationale for using methanol/water as release medium was to complete degradation of the implants within reasonable time period. If using a standard buffer medium, the time needed to reach complete degradation of the implants is similar to that observed in vivo, i.e. more than 5 months.

Fig. 5i shows the surface sections of the original extruded and injection-molded L-PLA cylinders fractured perpendicularly to the longitudinal axis. In both samples, the fracture of a slide of the implant has lead to characteristically splinters due to the brittleness of the polymeric matrix. Cross-sections of polymer matrices had a disc geometry. The injection-molded implant surface was more homogeneous in appearance than the surface of the samples produced by extrusion.

After 1 h in the degradation medium (Fig. 5ii), both samples showed numerous cracks at their surface section (fractured perpendicularly to the longitudinal axis) and an increase in the outer surface roughness. In the injection-molded sample, the cracks seemed to propage concentrically to the outer surface of the sample, perpendicularly to the longitudinal axis, whereas in the extruded one, the cracks seemed to appear at random. The different structures did not yet show a significant diverse behavior in degradation. Samples subjected to the in vitro tests for 6 h (not shown) were more cracked on their surface section (fractured perpendicularly to the longitudinal axis) and the cracks increased in size. The outer surfaces were characterized by irregularities suggestive of degradation. By the loss of material from the surface only, both samples shrinked little in their dimensions.

After 24 h immersion (not shown), the core of the extruded sample was extensively fragmented and porous. In the injection-molded sample, the crack dimensions increased, but the matrix did not become porous. At this stage of degradation, it was no more possible to obtain proper implant slides, as the brittleness of the matrix was too important (the disintegration of the device started by a break of the structure prior to the real resorption, when only small forces were applied to the device). This phenomenon was more pronounced for the extruded implant than for the injection-molded one, due to porosity. This resulted in an increased surface for the extruded sample, which helped for a fast resorption. After 48 and 72 h (not shown), both samples showed the same characteristics than for 24 h, but more pronounced.

After 144 h immersion (Fig. 5iii), the cores of both samples showed significant differences: the extruded sample was extremely porous and extensively fragmented, whereas the injection-molded sample showed numerous cracks throughout the matrix, but without porosity.

With regard to the matrix, shearing forces generated between the die wall and the polymer melt during extrusion of the polymer lead to the formation of oriented polymeric chains in the extruded implant, which may increase the crystallinity and therefore the final mechanical properties of the object. On the other hand, solid-state extrusion of a polymeric element with chain orientation may lead to the fracture of polymeric chains at the surface or to the formation of defects in the composite, such as cracking, and, in consequence, reduce the final mechanical properties of the object.

During the injection-molding process, the polymeric mass is first plastizised and then injected under pressure in a defined mold. This process lead to chain orientation, but without cracks at the surface of the device. In addition, the higher temperature employed during injection-molding, in contrast to extrusion, may have improved the chain orientation, i.e. the crystallinity [14]. Thus, the differences in matrix degradation seen between both implant samples could be attributed to the percentage of crystallinity, which might be enhanced in the injection-molded sample. It has also been shown [28], that micropores result from the faster erosion of amorphous compared to crystalline polymer regions, after a couple of days of degradation. This phenomenon may explain the earlier porosity seen in the extruded samples versus the injection-molded ones. Another explanation for the differences in matrix degradation may be the density of the matrix. As described previously, the injection-molded samples are more dense than the extruded ones. This phenomenon may lead to an increase water uptake in

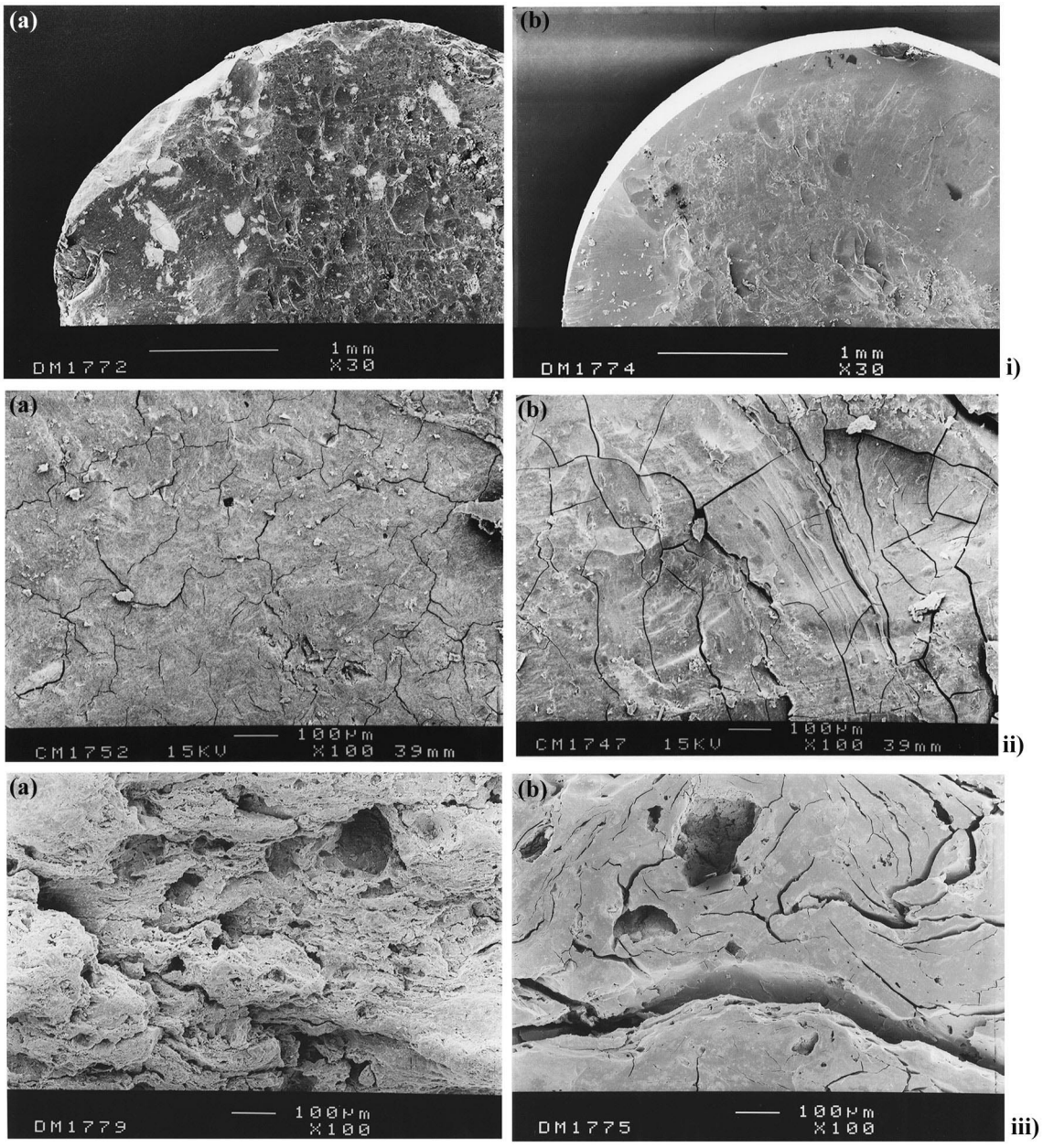


Fig. 5. Scanning electron micrographs of the extruded (a) and injection-molded (b) L-PLA samples, after fracture surface perpendicular to the longitudinal axis of the cylinder: (i) original samples, (ii) after 1 h immersion, (iii) after 144 h immersion.

the extruded implants, which may consequently accelerate the degradation process.

3.6. Evaluation of drug purity in the polymeric matrix after manufacturing and in vitro drug release from the implants

As most peptides are extremely unstable molecules, it has been very difficult to formulate and to deliver them without loss of purity. Indeed, during implant preparation, the peptide is exposed to various unfavorable conditions, in particular, exposure to high temperatures. Peptide purity right after extrusion and injection-molding has been evaluated. Before manufacturing, peptide purity was determined as being over 99.0% (depending on peptide content), whereas it was between 98.5 and 99.5% after extrusion and between 92.0 and 97.0% after injection-molding. The higher peptide degradation in the injection-molded samples may be due to the higher temperature and to the greater shearing forces employed during the manufacturing process. Strategies to reduce peptide degradation after injection-molding are based on an understanding of the effect of changes in the manufacturing conditions. These latter may be improved, by reducing peptide degradation, without interfering with the good manufacturing conditions.

Confirmation of the importance of matrix degradation was provided by drug release rate measurements.

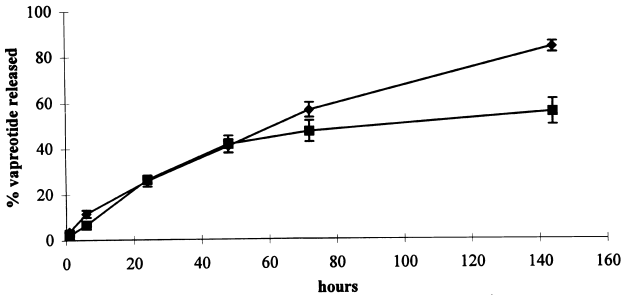


Fig. 6. In vitro drug release from the implants prepared by extrusion (-●-) and by injection-molding (-■-).

The initial rate of release of vapreotide from both implant samples, into the release medium, was almost the same; however, an increase in rate from 48 up to 144 h was observed with the extruded implants. These results are in good agreement with the scanning electron micrograph observations, since significant porosity appeared in the extruded implant after 24 h immersion. Indeed, as soon as the matrix begin to degrade, the drug is able to diffuse out of the matrix. Thus, an accelerated matrix degradation lead to an increased drug release Fig. 6.

Break of the extruded sample may have increased the degradation rate by increasing the surface of the sample. In order to assess the differences seen between the two in vitro drug release profiles, in vivo measurements should be undertaken. As the body tends to completely isolate foreign implants by forming a sheath-like fibrous membrane capsule around the implant [29], the possibility of braking for the extruded sample may be diminished in vivo. Thus, different in vivo release profiles should only be due to differences in matrix degradation, i.e. in the manufacturing method.

4. Conclusion

To date, extrusion has been the most commonly method used for the manufacturing of biodegradable implants for drug delivery. This is an easy manufacturing technique, which offers some advantages such as requiring only a small amount of raw material and needing low temperatures for preparation, which results in almost no peptide degradation. However the development of an injection-molding technique is more appropriate for large scale industrial production. Indeed, this manufacturing method ensures a good mixing treatment between polymer and drug and allows the manufacture of implants of various shapes. A partial material sterilization is also sometimes possible [24]. However, injection-molding presents some disadvantages, such as higher temperatures for preparation, larger amounts of raw material for initial trial and much higher loss of material during manufacture, compared to extrusion. This more complicated technique might also lead to little degradation of the active compound.

It has been demonstrated that both extrusion or injection-molding were possible methods for implant manufacturing. The most important difference seen between these two methods, was the rate of vapreotide release in vitro, which was increased in the extruded implants. This difference was assigned to the density of the matrix and to the crystalline/amorphous ratio, which is supposed to be increased in the injection-molded implants, due to the specificity of the manufacturing process. Scanning electron microscopy studies of the samples, during the in vitro test, were in good accordance with the rate of drug release.

This study has shown that the manufacture of biodegradable implants as drug delivery system by the mean of the injection-molding technique, was feasible. However, depending on the physico-chemical properties of the drug to be incorporated, the conditions used during the process have to be adapted, so as to limit drug degradation.

Ram extrusion has proved his efficiency in manufacturing peptide implants [30], but the development of an injection-molding technique for these devices may open new possibilities for the scaling up of extrusion. In addition, as injection-molding forms polymers into detailed designs of rods, it would allow the manufacture of implants of various shapes, in contrast to extrusion.

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