Macromol. Symp. **2005**, *224*, 93-104

Hydrostatic Extrusion of Poly(L-Lactide)

*Fengzhe Jin, Sung-Il Moon, Sadami Tsutsumi, Suong-Hyu Hyon**

Institute for Frontier Medical Science, Kyoto University
53 Kawara-cho, Shogoin, Sakyou-ku, Kyoto 606-8507, Japan

Summary: Poly-L-Lactide(PLLA) has been used as a bone fracture fixation material for several years. However, its mechanical properties are still not satisfied. To improve its mechanical properties, we examined the hydrostatic extrusion procedure on the PLLA rods made by Injection Molding process. The extrusion ratio was adjusted to 3, 6, 9, and 12. The molecular weight of the PLLA decreased from 260,000 to 200,000 after injection molding process, but it did not change during the hydrostatic extrusion procedure. The melting point of PLLA hydrostatic extrusion products were increased with the extrusion ratio, but the increment was not obviouse. Extrusion products having low extrusion ratio had α-form crystal in them, extrusion products having high extrusion ratio had both of α and β-form crystall in them. At extrusion temperature of 145°C, PLLA rods showed the best flowing trends in the pressure medium of PEG 400. Extrusion temperature is placed in the range of crystalline transition temperature and melting point of PLLA. At extrusion ratio 9～12, the extrusion products showed the best mechanical properties. The highest bending strength of the extrusion product was over than 350MPa. It is far stronger than that of the human cortical bone (200MPa). SEM observations showed that the fiber structure began to appear at an extrusion ratio ER=3, and at the extrusion ratio ER=6, the chain axes of PLLA became aligned to the extrusion direction. The structure of extrusion products at the high extrusion ratio showed highly oriented fiber structure composed of micro-fibril. At high extrusion ratio tranformation from α-crystal to β-crystal was also observed.

Keywords: biodegradable; extrusion; high strength; hydrostatic; orientation; poly(L-lactic acid)

Introduction

Metallic implants are commonly used for internal fixation of bone fracture fixation. More recently, ceramic implants have also been introduced in this field $^{1-6)}$. But in the recent two decades, bioresorbable polymer have made inroad in this field $^{7-20)}$.

Bioresorbable polymeric devices have a potential to replace metallic implants due to the following advantages:

(i) No need of reoperation for removal.

(ii) No restriction of bone growth owing to the gradual decrease in mechanical strength.

DOI: 10.1002/masy.200550609

(iii) Less risk of osteoporosity caused by stress-shielding due to excessive high strength such as with metallic devices.

(iv) No tissue reaction caused by metallic corrosion.

Many kinds of bioresorbable polymers have already been developed and clinically used in orthopedic, craniofacial and oral-maxillofacial surgeries. These completely bioresorbable polymers can generally be divided into two categories: semi-crystalline polymers, which have high strength, and amorphous polymers, which have low strength. A higher initial strength than natural bone and retention of this strength until the bone heals is required in practice.

Among bioabsorbable fixation device materials, poly-L-lactide (PLLA) tends to be used more frequently than that of other biodegradable polymers. It is because PLLA has appropriate mechanical properties and can be readily synthesized by poly-condensation of L-lactic acid and the ring-opening polymerization of L-lactide.

Poly-L-Lactide has been used as a bone fracture fixation material for several decades although its mechanical properties are still not satisfied7-19). Hydrostatic extrusion as a kind of solid-state extrusion had been applied to non-degradable polymers21-30). Compare to ram solids state extrusion, hydrostatic extrusion can obtain products having fine surface than that of ram solid state extrusion due to self lubrication of the pressure medium.

In a previous report 20), we have briefly introduced hydrostatically extruded PLLA that retained the high strength of the polymer. In this report, we wish to report in more details on the processing conditions of hydrostatic extrusion, and some new properties of hydrostatically extruded PLLA.

Experimental Details

1. Polylmerization of PLLA

Ring-opening polymerization of L-lactide was conducted in the bulk as we reported before7). Briefly, stannous octoate(tin[Ⅱ]2-ethylhexanoate) was used as the catalyst, the desired monomer(L-lactide) and an ethyl ether solution of the catalyst were placed in Pyrex glass tube, which was sealed after evacuation to 0.133Pa. The sealed tubes were then placed in a silicone oil bath maintained at 160℃ for 24hr. The polymerization product was dissolved in dichloromethane and precipitated with methanol to purify the polymer. The polymers that was obtained from the polymerization were processed to pellets for the next step.

Pellets of purified PLLA having an initial viscosity average molecular weight 260,000 (Tm=170~180°C) were dried under the vacuum conditions before melt processing.

2. Injection Molding of PLLA

The PLLA we synthesized by ring-opening polymerization, was tested by Melt Flow Index (MFI, CFT-20, Shimadzu, Co., Japan) to determine the best injection molding conditions. Briefly, 1.5g samples were put into the extrusion container, and 39 N force was applied on the samples. Temperature range was between 150°C to 300 °C, and 6°C/min heating rate was applied. Samples were melt extruded from a $\Phi = 1.2$mm die with a diameter of 1.2 mm.

To obtain the PLLA rods, suitable for hydrostatic extrusion machine, we injection molded the PLLA pellets to the rods having length of 100mm and diameter of 10mm, 15mm and 20mm, separately. The injection molding of PLLA proceeded under the following condition: nozzle temperature 200°C; cylinder temperature 190°C; mold temperature 40°C; first stage pressure 100MPa and second stage pressure 160MPa (ES400, Nissei Plastic Industrial Co., LTD.).

3. Hydrostatic Extrusion of PLLA

The hydrostatic extrusion machine was designed by ourselves, and was made by Kenkosha (Kyoto, Japan). Hydrostatic extrusion of PLLA rods made by injection molding were extruded under the temperature range of 130°C~165°C. At every extrusion temperature we also changed the extrusion ratio from 3 to 12. The extrusion cylinder was filled with polyethylene glycol 400 (PEG 400, Nacalai Tesque Inc.) as the lubricating oil. It can also work as the pressure transfer media during the hydrostatic extrusion.

4. The measurement of the physical properties of hydrostatically extruded products

The changes in the average molecular weight of PLLA was tested by GPC (C-R4A GPC System, Shidadzu Co., Japan), using polystyrene (PS) as the standard and chloroform as the eluent.

Flexural properties of PLLA were tested by Autograph SD-100-C (Shimadzu Coporation, Kyoto, Japan) using the three points test method described in ASTM D796.

Flexural strength and flexural modulus were calculated from following equations:

$$\sigma_{\max} = \frac{8F_{\max}L}{\pi d^3} \qquad \mathrm{E} = \frac{4L^3}{3\pi d^4} \bullet \frac{E}{Y}$$

σ_{max} (N/m^2): Flexural Strength
Fmax(N) :Maximum Force
L(m): Support Span
d(m): Diameter of Test Piece

E(N/m^2): Flexural Modulus
E/Y(N/m): The gradient of F/X curve
L(m): Support Span
d(m): Diameter of Test Piece

Thermodynamic properties of PLLA were tested by DSC (DSC6200, Seiko Instrument, Japan), using Al_2O_3 as the standard. 10mg samples were used for measurement, and temperature range was between 25℃～250℃, using a heating rate of 10℃/min.

Dynamic mechanical thermal properties were measured by a viscoelastic analyzer (Rheogel-E4000, UBM Co. Ltd. Japan). The storage modulus(E') and the loss modulus(E") were measured as a function of temperature from 25 to 200℃ at 2℃/min. The continuous sine wave was performed at the base frequency of 10Hz.

Scanning Electronic Microscopy (SEM, S-2380 Hitachi, Ltd., Japan) was used to observe the surface conformation of the cross-section of extrusion products.

Wide-angle X-ray scattering profiles were recorded with Ni-filtered Cu Ka radiation generated at 40 kV and 55 mA on a Philips X'Pert MRD (Philips Analytical In. Japan) rotating anode X-ray generator equipped with a diffractometer and a pulse height discriminator.

5. *in vitro* degradation of hydrostatic extrusion products

In vitro test were taken place in phosphate buffer solution (PBS, pH=7.4). The mean molecular weight change and bending strength changes at various hydrolysis time were tested. The PBS buffer was changed weekly to avoid the effect of degraded acidic products from samples.

Results and Discussions

1. Injection Molding of PLLA

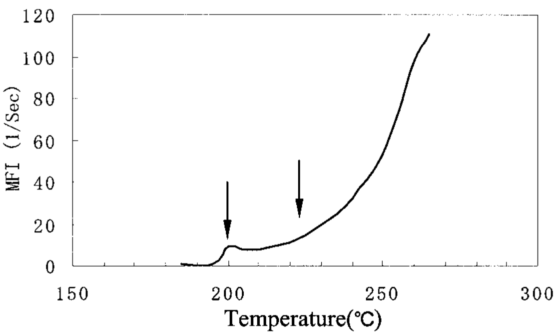


Figure 1. Melt flow index of synthesized PLLA.

The injection molding of polymers is normally performed under a temperature which is higher than their melting point. The PLLA we synthesized had the melting point of 176°C, thus, the injection molding must be conducted over this temperature. But high temperature over 250°C is known to cause thermo-decomposition of biodegradable polymers. So we need to decide the preferred injection molding temperature of PLLA. Melt Flow Index was used to determine it. As shown in figure 1, the PLLA we synthesized (having Mw of 280,000) showed a stable state between 200°C~215°C. To avoid the decomposition of the polymer during high temperature processing we selected 200°C as the injection molding temperature of PLLA.

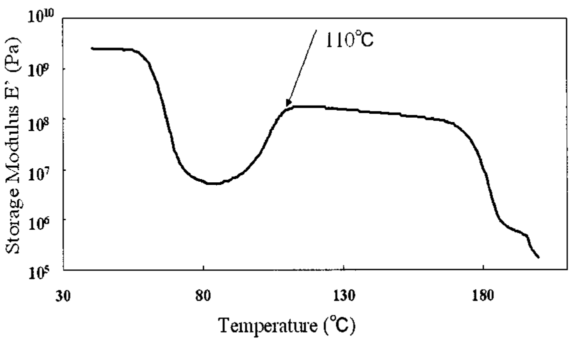


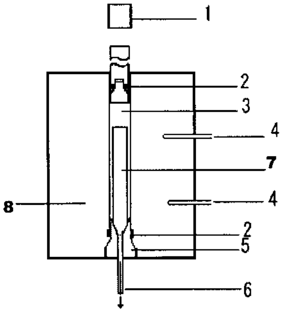
Figure 2. Dynamic mechanical thermal analysis injection molded PLLA.

Injection molded PLLA rods were transparent and had a flexural strength of 120MPa and a flexural modulus of 1.5 GPa. It is somewhat higher than that of melt extruded materials. It resulted from the remaining of the stress generated by high speed flow into the mold. Because the temperature of the mold was fixed at 40°C, such stress can be introduced. For comparison, using injection molding process, the molecular weight of PLLA was degraded from 260,000 to 200,000, because of heat decomposition.

2. Hydrostatic extrusion of PLLA

According to S. M. Aharoni[25], R. S. Porter[26-28], and M. Takayanagi[21, 29-30]'s research, successful solid-state extrusion can only occurs in semi-crystalline polymers and crystalline relaxation of the polymer is needed. The solid-state extrusion of polymer can be proceed under condition of Tc (Crystalline Transition Temperature) < Te (Extrusion Temperature) <Tm (Melting Point)[25]. Hydrostatic extrusion is also a solid-state extrusion, so conditions must be selected according to this rule. Figure 2 indicates the dynamic mechanical thermal properties (DMTA) of injection molded PLLA. We can see from this figure that the PLLA we produced has a crystalline transition temperature of 110°C (also can be seen in figure 6, curve ①) and a melting point of 176°C (See figure 6 curve ①). So we can assume that the hydrostatic extrusion temperature range is 110°C<Te<176°C. In our experiments, we selected a temperature range between 130°C~165℃, because of the pressure limitation of our hydrostatic extrusion machine. The hydrostatic extruded rods had higher flexural strength than the rods produced by injection molding, and their strength increased with the extrusion ratio.

Like we show on figure 3, hydrostatic extrusion has some advantages than that of ram solid state extrusion, by applying pressure medium (3) during solid state extrusion, the frictional force between the container (8) and billets (7) can be avoided, and the force around the samples was homogeneous, which would eliminate cracking on the surface and the internal parts of the samples. The surface of hydrostatic extrusion products only depends on the surface of the extrusion die (5). It means that, if we can use a die with smooth surface, the final products will be smooth and if the die has a rough surface, the surface of the final products will also be rough. The



1. Plunger (Supply the pressure on the pressure medium)
2. Higher pressure sealer
3. Pressure medium (PEG400)
4. Temperature sensor
5. Extrusion die
6. Extruded products
7. Cylindrical billet (Injection Molding Products)
8. High pressure container

Figure 3. Schematic View of Hydrostatic Extrusion Machine.

extrusion ratio of extrudate(6) was determined by divide perpendicular cross section area of cylindrical billet (7) with the cross section area of extruded products (6).

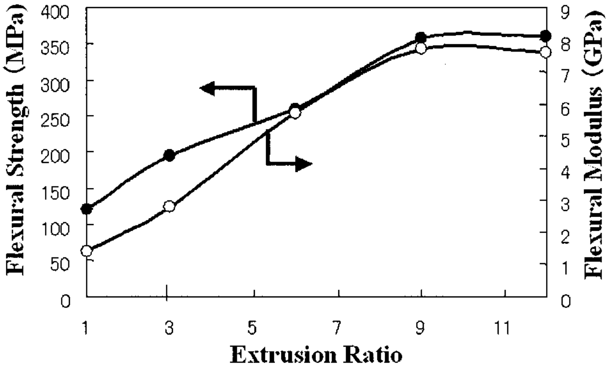
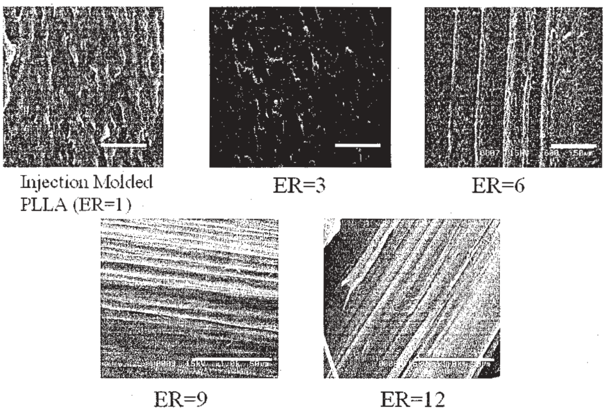


Figure 4. Extrusion ratio dependence of the flexural strength and flexural modulus of hydrostatically extruded PLLA. (Extrusion Temperature 145°C)
(●: Flexural Strength ○: Flexural Modulus).

Figure 4 shows the flexural properties of the rod we hydrostatically extruded at 145°C in different extrusion ratio. The flexural strength of hydrostatically extruded PLLA was increased with the increment of extrusion ratio (ER). The extrusion products prepared by extrusion ratio of 3, had similar flexural strength to that of human cortical bone (200~230MPa), and over this point, the strength increased with the extrusion ratio. Highest flexural strength (350MPa) was obtained when the extrusion products had an extrusion ratio between 9~12. For the flexural modulus, although it was also increased with the increasing of extrusion ratio, the maximum value was 7.5GPa, which is still lower than that of human cortical bone (7~14GPa).



Injection Molded PLLA (ER=1)

ER=3

ER=6

ER=9

ER=12

Figure 5. SEM observation of the cross-section of hydrostatically extruded PLLA. (The white bar on the picures indicates the length of 50μm).

Such an enhancement of strength resulted from the orientation of PLLA crystal lamella is apparent from both DSC measurements and SEM observations. DSC results indicates that after hydrostatic extrusion, the crystallinity of PLLA was increased proportionately to the extrusion ratio. SEM observations of the cross-section of PLLA indicate that samples prepared by injection molding having ER 3, had no fibrous structure on it, but when the ER increased to 6, the micro-filament structure appeared on cross-section and it further increased with increasing of extrusion ratio. No obvious differences were observed in the samples when the hydrostatic extrusion products was between ER 9 and 12.

Accompanied with the increases in the extrusion ratio, the melting point and heat of fusion of PLLA was also increased, the extrudate with an ER of 3 and 6 didn't shown a peak around 168 °C in addition to the main peak around 180 °C due to the melting of α-crystals (curve ② , ③). The extrudates with the higher ER of 9 and 12 exhibited two peaks around 168 °C and 182°C due to the melting of β crystals and α crystal (Curve ④, ⑤). The ratio between β-form and α-form increased slightly with the increasing of ER31).

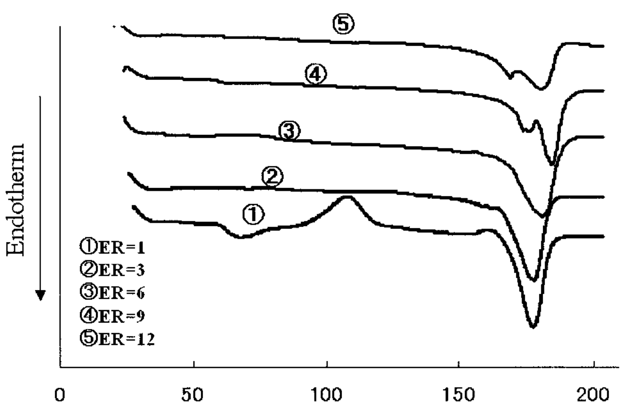


Figure 6. Thermodynamic properties of hydrostatically extruded PLLA having different extrusion ratio.

The WAXD results in figures 7 show that instead of amorphous state of injection molded PLLA, the intensities of reflections from hydrostatically extruded products were progressively increased with ER (①~⑤). It means that PLLA crystals were formed because of orientation of PLLA lamella, and crystallinity of them was increased by extrusion ratio ER. Furthermore, at high extrusion ratio, some of the peaks related to α-crystals were weakened (exp. hkl (306), $2\theta=31.3$), and some of the peaks related to β-crystals (hkl 203, $2\theta=33.2$) of PLLA were enhanced because of the transformation of crystals from α-from to β-form. 31, 32) It was another evidence for the formation of β-crystal PLLA during hydrostatic extrusion.

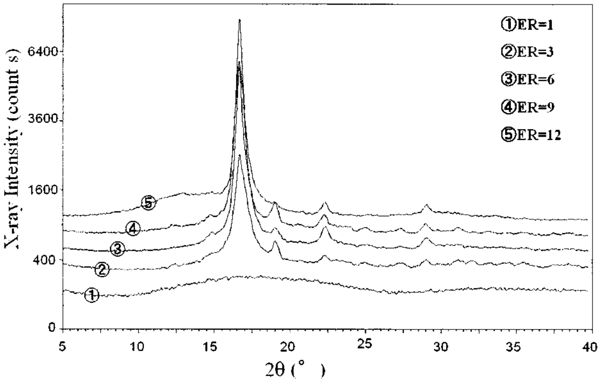


Figure 7. WAXD profile for an series of PLLA prepared by hydrostatic extrusion at 145℃. Here ER=1 indicates injection molded PLLA, ER=3 to 12 indicates hydrostatic extrusion products having related extrsusion ratio.

3. *In vitro* degradation of hydrostatic extrusion products

Strength retention of hydrostatically extruded products are shown on figure 8. We selected the hydrostatic extrusion products having its extrusion ratio ER=9 as the test samples. As can be seen from the data in this figure the flexural strength of hydrostatically extruded PLLA products was maintained over the strength of human cortical bone (200~230 MPa) for about 16 weeks. Furthermore, the flexural modulus was

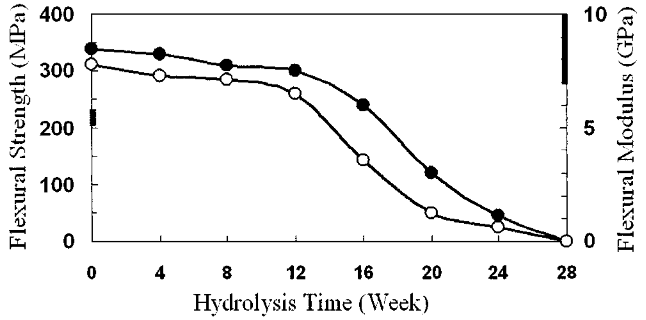


Figure 8. Retention of flexural strength and flexural modulus of hydrostatic extrusion products (ER=9) of PLLA during hydrolysis in PBS solution (pH=7, 37°C). Thick bar on the figures indicate the flexural strength (200~230MPa) and flexural modulus(7~14 GPa) of human cortical bone. (●: Flexural Strength ○: Flexural Modulus).

kept very close to that of human cortical bone (7~14GPa) during the same period of time. It is well known that, bone fracture needs 3 to 6 months to be completely recovered. The retained strength of the hydrostatic extrusion products (ER=9) fully fits these required conditions as bone fixation devices. Although the kink band formation will occurs in highly compacted firbro structure reinforced materials, hydrostatically extruded PLLA still remaining some amorphous region can work as cushion of the compress compact to avoid the failure from them.

Relative molecular weight change of hydrostatic extrusion products is shown in figure 9. The apparent molecular weight of PLLA decreased rapidly in the first 16 weeks, but after 20 weeks degradation, it did not change as much. By calculating the real molecular weight and combining the results of figure 6, we can find that products having molecular weight lower than 60,000 (200,000 × 30%) lose their strength during hydrolysis in PBS. Slower molecular weight decreases in a later stage indicates that the crystalline regions in the products mainly remained and complete degradation will require more time.

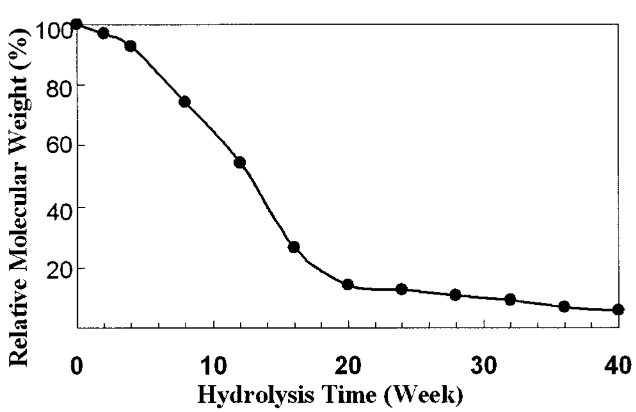


Figure 9. Molecular weight changes of hydrostatic extrusion products during the hydrolysis in PBS showed that molecular weight of PLLA was decreased fastly in the early stage (16 weeks). But after 20 weeks degradation, the decreasing in molecular weight became slower.

Conclusions

Hydrostatic extrusion of PLLA was successfully conducted at a temperature of 145°C.

Hydrostatically extruded products showed the higher strength than that of injection molding products and melt extrusion products. The maximum value of flexural strength and flexural modulus was 350 MPa and 7.5 GPa, respectively. The former value is significantly higher than the value of human cortical bone and the later value is near the value of human cortical bone. The strength of hydrostatic extruded products was remained for 16 weeks after immersion in PBS solution at 37°C. This time period is sufficiently long for bone healing.

The high strength of hydrostatic extrusion products was due to the orientation of PLLA lamella during the extrusion process. DSC results indicate an increase in the melting point and the heat of fusion. Both of α-form and β-form crystal were formed at the high extrusion ratio.

WAXD profile indicates that crystals of PLLA were formed during hydrostatic extrusion, transformation from α-form to β-form crystals was also observed at high extrusion ratio.

SEM observations showed a fibrous structure on the cross-section of the hydrostatic extrusion products.

[1] Uhthoff HK., and Dubuc FL, Bone structure changes in the dog under rigid internal fixation. *Clin Orthop Rel Res* **1971**; *81*: 165-170.

[2] Champy M., Lodde JP., Kahn., and Kielwasser P, Attempt at systematization of the zygomatic bone : 3. techniques and results. *J Otplatyngol* **1986**; *15*: 39-43.

[3] Akeson. WH., Woo SLY, Rutherford L, Coutts RD, Consalves M, and Amiel D, The effects of rigidity of internal fixation plates on long bone remodeling. *Acta Orthop Scand* **1976**; *47*: 241-249.

[4] Tonino AH, Davidson CL, Klopper OI, and Linctan LA, Protection from stress in bone and its effects. *J Bone Jt Surg* **1976**; *588*: 107-113.

[5] Woo SLY, Simon BR, Akeson WH, and Murray MP, An interdisciplinary approach to evaluate the effect of internal fixation plate on long bone remodeling. *J Biomechan* **1977**; *10*: 87-95.

[6] Paavolainen P, Karaharju E, Statis P, Ahonen J, and Holmstrom T, Effect of rigid plate fixation on structure and mineral content of cortical bone. *Clin Orthop* **1978**; *136*: 287-293.

[7] Hyon SH, Jamshidi K, and Ikada Y, Synthesis polylactides with different molecular weights. *Biomaterials* **1997**; *18*: 1503-1508.

[8] Hyon SH, Jamshidi K, Ikada Y, Effects of the residual monomer on the degradation of DL-lactide polymer. *Polym Intern* **1998**; *46*: 196-202.

[9] Getter L, Cutright DE, Bhaskar SN, and Augsvurg JK, A biodegradable intraosseous appliance in the treatment of mandibular fractures. *Oral Surg* **1972**; *30*: 344-348.

[10] Vert M, Chabot F, and Christel P, Stereoregular bioresorbable polyesters for orthopedics surgery, *Makromol Chem Suppl* **1981**; *5*: 30-41.

[11] Tunc DC, Rohovsky MW, Lehman WB, Strongwater A, and Kummer F, Evaluation of body absorbable bone fixation devices. *Proc. 31 st Annual Orthop. Res. Soc. Las Vegas, Nevada, Usa*, January **1985**; *165*.

[12] Schindler A, and Haroer D, Polylactide. II. Viscosity-molecular weight relationships and unperturbed chain demensions. *J Polym Sci Chem Ed* **1979**; *17*: 2593-2599.

[13] Leenslag JW, Pennings AJ, Bos RM, Rozema FR, and Boering G, Resorbable materials of poly(L-lactide). VI. Plates and screws for internal fracture fixation. *Biomaterials* **1978**; *8*: 70-73.

[14] Hope PS, and Parsons B, Manufacture of High Stiffness Solid Rods by the Hydrostatic Extrusion of Linear Polyethylene. Part 1: Influence of Processing Conditions. *Polym Eng Sci* **1980**; *20*: 589-596.

[15] Fischer EW, Sterzel HJ, and Wegner G, Investigation of the structure of solution grown crystals of lactide copolymers by means of chemical reaction. *Kolloid-Z.u.Z. Polymer* **1973**; *251*:980-990.

[16] Cam D, Hyon SH, and Ikada Y, Degradation of high molecular weight poly(L-lactide) in alkaline medium. *Biomaterials* **1995**; *16*: 833-843.

[17] Santis PD, and Kovacs S, Molecular Conformation of Poly(L-lactic Acid). *Biopolymers* 1968; 6: 299-306.

Eling B, Gogolewski S, and Pennings AJ, Biodegradable materials of poly(L-lactic acid): 1. Melt-spun and solution-spun fibres. *Polymer* **1982**; *23*: 1587-1593.

[18] Hyon SH, Jamshidi K, and Ikada Y, Melt spinning of poly-L-lactide and hydrolysis of the fiber in vitro. *Polymers as biomaterials, Ed. Shalaby W. Shalaby, Plenum Press* **1983**; 51-65.

[19] Jin FZ, Hyon SH, Iwata H, Tsutsumi S, Crosslinking of poly(L-lactide) by γ-irradiation, *Macromol. Rapid. Commun.* **2002**; *23*: 909-912.

[20] Hyon SH, Jin FZ, Jamshidi K, Tsutsumi S, Kanemoto T, Biodegradable Ultra High Strength Poly(L-lactide) Rods for Bone Fixation, *Macromol. Symp.* **2003**, *197*, 355-368

[21] Nakamura K, Imada K , and Takayanagi M, Solid-state extrusion of isotactic polypropylene through a tapered die: 2. Structure and some properties of extrudates. *Polymer* **1974**; *15*: 446-450.

[22] Ariyama, T. Effects of hydrostatic extrusion on the mechanical and thermal properties of polypropylele, *Journal of Materials Science*, **1996**; *31*: 3813-3819.

[23] Nakayama K., Kanetsuna H., Hydrostatic extrusion of solid polymers, *Journal of Materials Science*, **1975**; *10*: 1105-1118.

[24] Shahin M.M, Olley R.H, Bassett D.C., Maxwell A.S, Unwin A.P., Ward I.M., Morphological changes in pressure annealed polyethylene, Journal of Materials Science, **1996**; *31*: 5541-5549.

[25] Aharoni S.M., SIBILIA J.P., Conformational behavior and solid-state extrudability of crystalline polymers, *Polymer engineering and science* **1979**; *19 (6)*: 450-455

[26] Lee Y.C, Porter R.S., Crystallinzation of poly(ether ether ketone) orientated by solid-state extrusion, Macromolecules **1991**; *24(12)*: 3527-42

[27] Kim B. S., Porter R.S., Uniaxial draw of poly(ethylene oxide) by solid state extrusion. *Macromolecules* **1985**; *18(6)*: 1218-21

[28] Southern J.S, Capiati, N.J., Kanamoto T., Porter R.S., Zachariades A.E., Solid state extrusion. *Encycl. Polym. Sci. Eng.* **1989**; *15*: 346-62

[29] Imada K., Takayanagi M., Plastic deformation of high deisity polyethylene in solid state extrusion. *International Journal of Polymeric Materials* **1973**; *2(2)*: 105-24

[30] Maruyama S., Imada K., Takayanagi M. Application of upper bound theory to solid state extrusion of polymers. *International Journal of Polymeric Materials* **1973**; *2(2)*: 125-36

[31] Sawai D., Takahashi K., Imamura T., Nakamura K., Kanamoto T., Hyon S.-H., Preparation of oriented β-form poly(L-lactic acid) by solid-state extrusion. *Journal of Polymer Science, Part B: Polymer Physics* **2002**; *40(1)*: 95-104

[32] Brizzolara D., Cantow H.-J., Diedirichs K., Keller E., Domb A. J., Mechanism of the Stereocomplex Formation between Enantiomeric Poly(L-lactide)s. *Macromelecules* **1996**; *29*: 191-197