Biodegradable Ultra High Strength Poly(L-lactide) Rods for Bone Fixation

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Summary: The hydrostatic molecular orientation technique was used to explore the highest mechanical improvements achievable for poly-L-lactide (PLLA). The mechanical attributes of these materials designed for bone fracture fixation devices, i.e. bending strength and modulus were measured and compared with those prepared by stretching method. The starting samples were prepared by conventional melt extrusion at 200 °C followed by hydrostatic extrusion at 140 °C using glycerin filled extruder. Uniaxially stretched rods were prepared by drawing in silicon oil at 120 °C. The physical properties of these rods are inadequate as mechanical supports in the dynamic healing process of the bone. Moreover, they underwent a marked strength deterioration when immersed in aqueous buffered solution for 90 days. On the other hand, the hydrostatic extrusion technique produced rods with progressively higher bending strength that showed only a small drop after 90 days hydrolytic degradation. Micrographs suggested a superior molecular orientation and packing, which could be associated with the improved performance. The hydrostatic extrusion technique proved to be a safe and effective approach for strengthening biodegradable polymeric materials for dynamic mechanical support in orthopedic medical devices.

Keywords: bone fixation; hydrostatic extrusion; poly(L-lactide) rods, ultra high modulus; ultra high strength

Introduction

Metallic devices are commonly used in orthopedic fracture fixation surgery. Many ceramics have also been introduced to this field in recent years [1,2)]. The most recognizable advantage of these materials is their high bending/twisting modulus, or their "stiffness". Their versatile machinability might be another positive attribute. Although the brittleness of ceramic materials can be of concern, excessive stiffness can cause refracturing of the reconstructed bone. This effect can be attributed to the possibility that such bone is inadvertently prevented of absorbing the

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torsional/bending energy generated during the normal human physical activities [3-5]. Removal of such devices by follow-up surgery remedied this situation. Despite all innate risks, the second surgeries also helped alleviating concerns over ionic leachables from metallic devices in long term implantation [6].

Based on the above observations, one would be encouraged to design fracture fixation devices from materials with elastic modulus equal or slightly higher than that of human cortical bone. Since it is known that appropriate mechanical stimuli enhance completion of the bone healing process, materials with controlled degrading strengths will also assure a natural transfer of dynamic load to the healing bone. If such materials afford minimum process susceptibilities and safely disappear when their functions have diminished, the concerns over the consistency of product initial quality and the need for follow-up removal surgery will also subside.

Polymers of lactic acid have enjoyed remarkable amount of attention in last few decades [7-19]. Their polymeric nature allows for a wide spectrum of property modulation by synthesis (e.g. molecular weight[7]) and processing (e.g. molecular orientation techniques[13, 18]). Lactic acid exists in two optical isomers, i.e. L and D. Polymers of uniform optical isomers have higher level of molecular regularity compared to those of racemic equal-mixture of isomers [8].

The fact that most designers investigating orthopedic devices have chosen poly-L-lactide (PLLA) is reflective of the above considerations. Cutright et al.[9] used PLLA plates in the treatment of mandibular fractures in the dog. The efforts of Vert et al.[10] to improve mechanical performance via synthesis resulted in a PLLA with a bending modulus of 3.4 GPa. Tunc et al.[11] raised the bar to 5.2 GPa. A composite bone plate of latide-glycolide copolymer made by Schindler et al.[12], having a low bending strength of 265 MPa and its rapid fall due to *in vitro* hydrolytic degradation diminished its strength in one month. Pennings et al. [13] achieved 5 GPa bending modulus by succeeding in the synthesis of PLLA of a viscosity average molecular weight of about one million. Higher molecular weights, however, generally complicate familiar processing techniques that can reliably sustain such high molecular weights throughout the manufacturing.

This study attempts to develop "hydrostatic extrusion"[20] a new technique by which biodegradable polymer can be safely and reliable processed in order to enhance their mechanical properties and to meet the performance of support devices in orthopedic trauma surgery. Some preliminary data indicating the positive influence of this technique not only on the mechanical properties of PLLA, but also on the suppression of hydrolytic degradation will be presented.

Materials and Methods

Polymerization

Ring-opening polymerization of L-lactide 7) was conducted in the bulk using stannous octoate (tin[II] 2-ethylhexanoate) as the catalyst. The dried monomer and an ether solution of the catalyst were placed in a Pyres glass tube, which was sealed after evacuation to 10^{-3} mm Hg. The sealed tubes were then conditioned in a silicone oil bath maintained at 160 °C for 24 hr. The polymerization product was dissolved in dichloromethane and precipitated with methanol to purify the polymer. Thus purified polymers were dried under vacuum.

Processing of PLLA Plates and Rods

Two PLLA samples with viscosity average molecular weights of $2.8 \cdot 10^5$ and $3.6 \cdot 10^5$ (melting point between 170-180°C) were prepared.

Compression molding: PLLA with lower Mw was kept in a hot press at around 210 °C for 5 min, followed by the application of a 250 kg/cm^2 pressure for an additional 5 min. Thereafter, the samples were cooled rapidly to obtain a 3 mm – thick plates of PLLA.

Uniaxial Stretching: The PLLA sample with higher Mw was put in an extruder under reduced pressure, then melt-extrusion molding was carried out from 200 to 220 °C. The cylindrical molded rods were uniaxially drawn to preset lengths inside silicone oil kept at 120 °C, followed by annealing at 140 °C for 30 min. The rods then were cut into test specimens.

Hydrostatic Extrusion: Melt extrusion products were subjected to hydrostatic extrusion as shown in Fig. 1 14) at 140 °C with an extrusion rate of 5.0 mm/min using a glycerin-filled extruder.

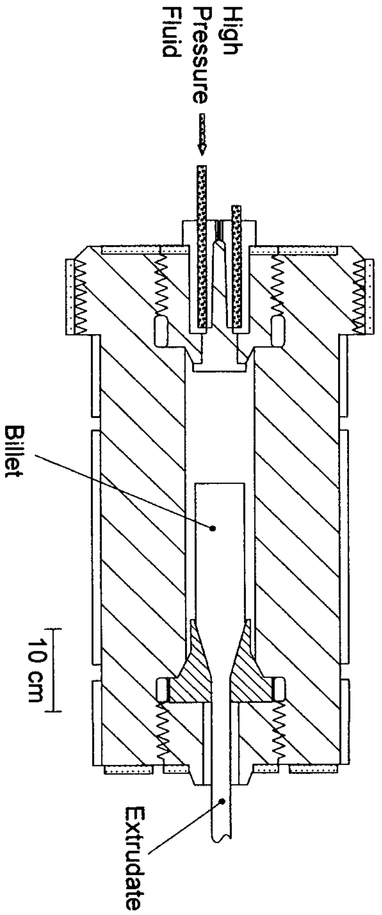

Figure 1. Cross-sectional view of the hydrostatic extruder used in the present study.

Measurement of Viscosity Average Molecular Weight

The viscosity-average molecular weight was calculated from the intrinsic viscosity $[\eta]$ according to the following equation (12):

$$[\eta]=5.45\cdot10^{-4}\,Mv^{0.73}$$

where [η] was measured in chloroform at 25 °C and Mv is the viscometric average molecular weight.

Measurement of Density

The density was measured at 30 °C by using a density gradient column of *n*-hexane/carbon tetrachloride system. Prior to the measurement, the test piece was deaerated by immersion for 30 min in *n*-hexane. The crystallinity was calculated from the measured density according to the following equation. [21)]

$$1/\rho=\chi/\rho_c-(1-\chi)/\rho_a$$

where, χ : crystallinity

ρ : measured density of the test piece

ρ_c : density of crystalline polymer (= 1.290 g/cm^3)[15)]

ρ_a : density of amorphous polymer (= 1.248 g/cm^3)

Tensile properties

Stress-strain curves were recorded on plates of 50 mm length at 100 %/min elongation rate with an Autograph SD-100-C (Shimadzu Co., Kyoto, Japan). The temperature and relative humidity were kept at 25 °C and 65 % RH, respectively.

Thermal properties

Thermal properties of PLLA samples were measured by a Shimadzu DT-50 differential scanning calorimeter (DSC) using Indium as standard. Heating was performed under nitrogen at 10 °C/min.

Measurements of Bending Strength

The bending strength of PLLA rods and plates were measured by the three-point bending method according to the Japanese Industrial Standard (JIS K7171) using an Autograph SD-100-C (Shimadzu Co., Kyoto, Japan). The cross-head speed was 10 mm/min, and the temperature and relative humidity were 25 °C and 65% RH, respectively. The bending strength was determined using the following equation:

$$BS = 8SL / \pi d^3$$

where BS = bending strength (MPa), S = strain (Nm), L = support span (mm), d = diameter of the specimen (mm).

Wide Angle X-ray Diffraction

X-ray diffraction patterns were recorded with a wide angle X-ray flat camera manufactured by Rigaku Denki Co. (Osaka, Japan), using Cu-kα (Ni filtered) at 50 KV and 80mA.

In Vitro Degradation Study

PLLA specimens were immersed in phosphate buffered saline (PBS, pH 7.4) regulated at 37 °C by using a polymer/solution ratio of 3g/10ml. The pH of solution was monitored to be stable through out 25 weeks experiment. Five specimens were removed from the PBS at 4-week intervals for monitoring changes in molecular weight and bending strength.

In Vivo Study

An *in vivo* study was designed to follow the plate biodegradation by using Japanese rabbits weighing 2.5 to 3.0 kg. After sterilization with ethylene oxide, the plate was intramuscularly or subcutaneously implanted in the back of the rabbit under aseptic conditions. Rabbits were allowed free movement and were given standard diet and care.

Results and Discussion

Compression Molding

It was necessary to control the compression molding temperature in a range from the melting point of the PLLA to 200 °C. Compression molding was difficult to carry out at a temperature below the melting point of the polymer. On the other hand, when performed at a temperature larger than 200 °C, the molecular weight of the PLLA drastically decreased to less than $2.0 \cdot 10^5$.

Conversely, by changing the thermal hysteresis during compression molding, we could obtain PLLA plates with the desired molecular weight.

The effect of the initial molecular weight of PLLA on the degradation rate was studied *in vitro* by monitoring changes in molecular weight, bending strength, and weight loss within hydrolysis time. Data relevant to PLLA plates having Mv of $7 \cdot 10^4$ and $2 \cdot 10^5$ are given in Figure 2. In both cases, the molecular weight drastically decreased initially, but the degradation rate of the higher molecular weight PLLA was lower than that of the lower molecular weight samples. A similar effect of molecular weight is also seen for the changes in strength and weight loss. It should be noted that hydrolysis through the second month virtually is not accompanied by reduction in bending strength for the plate prepared from PLLA with Mv of $2.0 \cdot 10^5$.

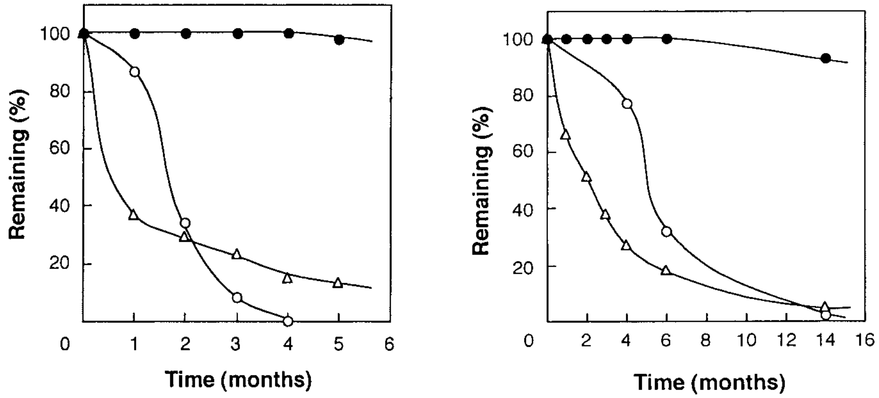

Figure 2. Molecular weight (△), bending strength (O), and residual weight (●) of PLLA plates having Mv $7 \cdot 10^4$ (left) and $2.0 \cdot 10^5$ (right) compressed at 220 °C as a function of hydrolysis time.

The *in vivo* tests were performed to study the influence of the implantation site on the biodegradation rates of PLLA plates having Mv of $7.0 \cdot 10^4$ and $2.0 \cdot 10^5$. The plates were implanted in two different sites, either intramuscularly or subcutaneously. The results of PLLA changes of molecular weight and bending strength are shown in Fig. 3. The effect of the implantation site was found to be insignificant at least in this study. On the contrary, the effect of initial molecular weight is remarkable, for the change of both the molecular weight and the bending strength. Figure

3 indicates that the molecular weight decrease of PLLA samples prepared by melt compression molding accelerated the degradation of the plate. The bending strength remained almost unchanged in case of PLLA plates with higher molecular weight, similar to what observed in the *in vitro* test, whereas the molecular weight of the lower molecular weight samples decreased to about 30 % of the initial value after the third month of implantation.

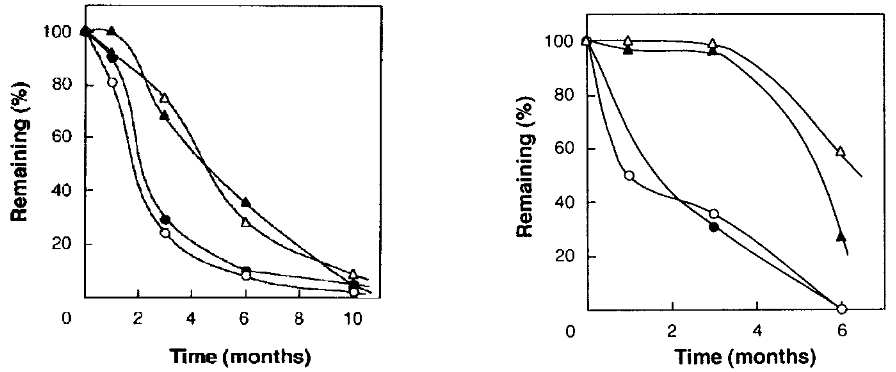

Figure 3. Molecular weight (left) and bending strength (right) remaining of PLLA plates with $7\cdot10^4$ (O) and $2.0\cdot10^5$ (△) initial molecular weight as a function of implantation time. Open symbols: subcutaneous implantation, closed symbols: intramuscular implantation.

It is clearly seen that the rate of decrease in molecular weight and bending strength are dependent on the initial molecular weight. Differences in the initial molecular weight of the polymers may influence the hydrolysis rate through differences in the glass transition temperature. Polymers with lower glass transition temperature have higher water accessibility which brings about higher rates of hydrolysis [16)].

Uniaxial Stretching

Since the molded PLLA plates obtained by melt compression molding had a viscosity average molecular weight of at least $2.0\cdot10^5$, they had a significantly high bending strength (170 MPa), but did not reach the desired bending strength of 220 MPa. Therefore, the molded PLLA rods were further subjected to uniaxial stretching in the extrusion direction in a silicone oil medium. Ideally, this treatment would realign polymeric chains and yield rods with improved bending strength.

Figure 4 shows the Wide Angle X-ray diffraction (WAXD) patterns of the rods drawn at 120 °C, followed by heat treatment at 140 °C in a fixed state. Clearly, crystalline orientation was observed even for the undrawn rod (the draw ratio being unity), but became more dominant as the draw ratio was increased. These results are similar to the PLLA fiber. The WAXD fiber diagram of PLLA has been also reported by other workers [17,18]. According to Pennings et al. [18], the oriented PLLA has two crystalline forms; the α form with a helical conformation and the β form with an extended helical conformation. Based on their findings, the diffraction pattern of the investigated PLLA rod seems to correspond to the α form.

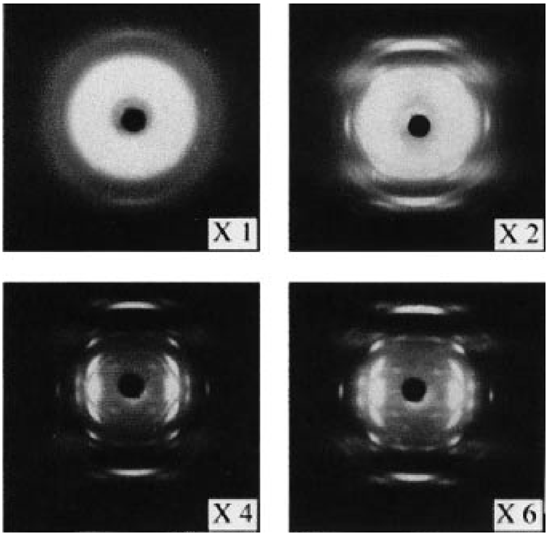

Figure 4. Wide angle X-ray diffraction patterns of the PLLA rods drawn at 120 °C, followed by annealing at 140 °C. The draw ratios are given in the photos.

The density and crystallinity of the rods drawn at 120 °C are plotted as a function of the draw ratio in Figure 5. The crystallinity of drawn PLLA rods was estimate from the observed density. As can be seen, the density as well as the crystallinity decreased as the draw ratio increased. Furthermore, these results differed from the PLLA fiber [18]. It is possible that voids were formed in the rods when drawn at 120 °C. The fusion curves obtained from DSC analysis for samples made by drawing in silicone oil at 120 °C and subsequent annealing are shown in Figure 6. As the

the draw ratio increased, the melting point where the major fusion occurs increased slightly. The shape of the endothermic peaks did not change to an extent indicator of a particular super molecular restructuring.

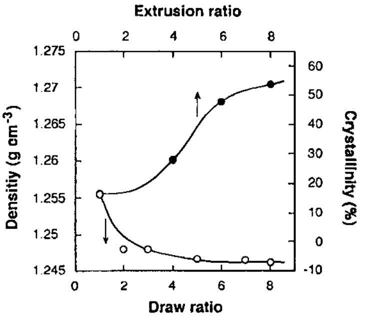

Figure 5. Density and crystallinity of the PLLA rods drawn at 120 °C. (O) or extruded at 140 °C (●).

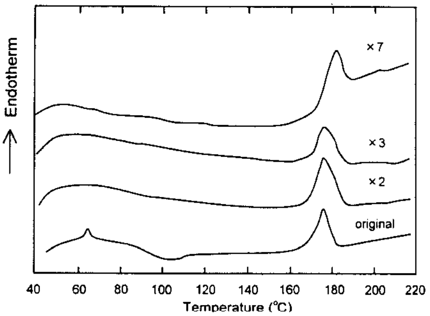

Figure 6. DSC thermograms of the undrawn PLLA rod and of PLLA rods drawn at 120 °C. Draw ratios are given in the figure.

Figure 7 shows tensile strength and Young's modulus of the rods drawn to different elongations, followed by annealing. It can be seen that rods of higher tensile strengths were obtained as the draw ratio became higher. These results are similar to those of the PLLA fiber [19)]. Bending strength and bending modulus of the rods drawn to different elongations are given in Figure 8. Both bending strength and bending modulus increased with the draw ratio, but tended to level off after a draw ratio of 5.

Although uniaxial stretching appeared to improve the physical properties compared to the untreated samples, this technique did not adequately improve the implant strength. It was nearly impossible with this technique to manufacture bone-fusing devices whose initial strength is comparable to that of devices made of stainless steel or ceramic. As described above, the density and bending strength of a rod obtained by drawing in a silicone oil bath at a draw ratio of 4 at 120 °C were 1.250 g/cm^3 and 250 MPa, respectively. These values indicate limitations of this technique. These unsatisfactory results may be attributable to the enlargement of small voids (which had been produced during molding) due to the drawing procedure at elevated temperatures after molding at normal pressures. This hypothesis is supported by the finding that the draw ratio does not boost a density representative of a molecular rearrangement. None of the previously proposed bone fracture fixation devices made of biodegradable PLLA had a density and bending strength higher than the above mentioned levels.

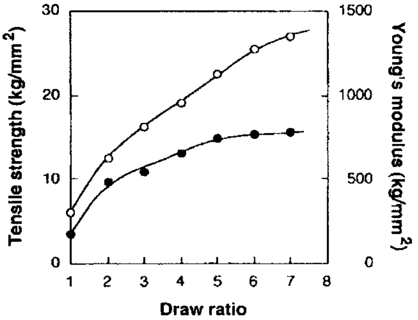

Figure 7. Tensile strength (O) and Young's modulus (●) of the PLLA rods drawn at 120 °C as a function of the draw ratio.

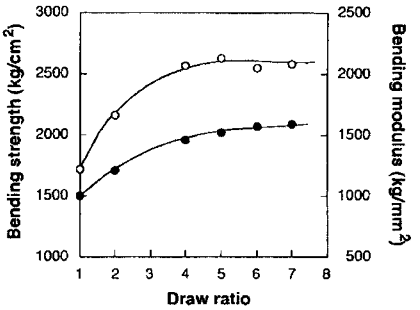

Figure 8. Bending strength (O) and bending modulus (●) of the PLLA rods drawn at 120 °C as a function of the draw ratio.

Hydrostatic extrusion

The present study was endeavored to provide a new approach toward bone fracture fixation devices made of biodegradable polymers such as PLLA that conceivably could have initial strengths comparable to those of similar devices made of stainless steel or ceramics. In addition, these implants should retain the necessary strength for the required time for osteosynthesis. Finally, such devices must rapidly lose their strength by means of hydrolysis and eventually be absorbed *in vivo* after the fractured bone reclaims its mechanical strengths.

To obtain rods for bone-fixation with high bending strength, the hydrostatic extrusion technique was proposed. The hydrostatic extrusion itself is a technique that has been used for non-biodegradable polymers [20)] such as polyethylene and polypropylene. However, there are no reports using biodegradable polymers such as PLLA. Furthermore, no published results were reported regarding the features of these products, including their strength preservation *in vivo*. This investigation revealed for the first time that bone fracture fixation devices with promising features can be produced by applying hydrostatic extrusion to biodegradable polymers.

The physical properties of the PLLA rods obtained by the hydrostatic extrusion are shown in table 1.

Table 1 The physical properties of PLLA rods obtained by hydrostatic extrusion method.

Extrusion Ratio	**Density (g/cm^3)**	**Initial Bending Strength (MPa)**
1	1.256	125
4	1.2601	272
6	1.2656	308
8	1.2705	340

Bending strength and density increased as the extrusion was increased. PLLA rods obtained by the hydrostatic extrusion had a high density (1.260 g/cm^3) and their bending strength was as high as 270 MPa at an extrusion ratio of 4. When the extrusion ratio was increased to 8, the density and the bending strength also rose to 1.271 g/cm^3 and 340 MPa respectively. Such a high density indicates that the products were free of crystal voids and cracks. These levels of bending strengths are comparable to those known for devices made of stainless steel or ceramics. To our knowledge, such a high bending strength has not been reported before for any devices made of biodegradable polymers such as PLLA.

In vitro evaluation of the treated samples was achieved by determining changes in their mechanical properties as a function of incubation time. The results of the in vitro hydrolysis test for uniaxially stretched and hydrostatically extruded PLLA rods are given in Figure 9. The products manufactured by drawing showed a marked decrease in their strength after 3 months of immersion. These products clearly could not retain a therapeutically adequate strength for the necessary time period. On the other hand, after 3 months immersion, the strength of the extruded samples deteriorated only slightly to approximately 250 MPa, maintaining over 85 % of their initial strength. This may suggest the absence of a catastrophic breakdown of these devices caused by 3 months *in vivo* hydrolysis. No meaningful difference in strength change was found between the *in vitro* and *in vivo* tests. Therefore, these devices seem to preserve the strengths necessary for 3 months support, a period which has been proposed to be necessary for bone restoration.

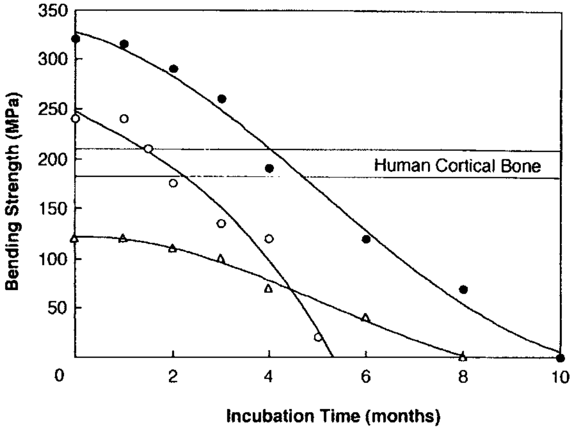

Figure 9. Bending strength loss of PLLA rods prepared by different methods as a function of incubation time at 37 °C in saline. (△): original, (○): drawn at 120 °C (draw ratio is 4), (●): extruded at 140 °C (extrusion ratio is 8).

Conclusions

Hydrostatic extrusion technique proved to produce resorbable PLLA articles with characteristic mechanical features never reported before. For instance, the molecular packing quality induced by this technique can prevent a premature hydrolytic deterioration of bending and modulus performance of the articles, which is imperative for the osteosythesis process.

By reviewing the above observations, we can confidently advance the hydrostatic extrusion technique as a viable approach in strengthening biodegradable polymers, such as PLLA, towards manufacturing of dynamic mechanical support systems in reconstructive surgeries. One can conceive such applications as bone screws, plates, and pins in oral, thoracic, and orthopedic restorative operations.