Nondegradative Microextrusion of Resorbable Polyesters for Pharmaceutical and Biomedical Applications: The Cases of Poly-Lactic-Acid and Poly-Caprolactone

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ABSTRACT: In recent years biodegradable polymers, particularly polyesters such as the poly(lactic acid) (PLA) and polycaprolactone (PCL), have gained high interests for their applicability in the biomedical and pharmaceutical fields where they're used for manufacturing various different resorbable devices, from tissue engineering scaffolds to controlled drug release systems. Despite many positive characteristics, processability of these materials still remains a critical issue as they easily tend to degrade during manufacturing. In this article we aimed to assess microextrusion as a nondegradative process for manufacturing PLA and PCL. The results we experimentally obtained, that are hereby presented, set a new point in the on-going debate on degradation during processing of resorbable polymers as they allow to affirm that microextrusion leaves unmodified molecular weight distributions without producing any evident reductions in mean molecular weight. Microextrusion thus represents a risk-free high molecular weight polymer processing solution for obtaining nondegraded products within pharmaceutical and biomedical production lines, such as for scaffolds for tissue engineering applications or drug delivery. © 2008 Wiley Periodicals, Inc. J Appl Polym Sci 108: 1591–1595, 2008

Key words: biodegradable; biological application of polymers; biomaterials; extrusion; polyesters

INTRODUCTION

In recent decades resorbable polymers have gained high interests in several different fields of application, from use in biomedical resorbable devices[1–13] to environment friendly plastics.[14,15] Among mostly used polymers, polyesters surely play a key role, particularly the poly(lactic acid) (PLA) and polycaprolactone (PCL) do. PLA is well known as one of the very first biodegradable materials used and it is currently applied in its medical grade for a wide range of productions from surgical sutures to matrices for tissue engineering, from active coatings to drug delivery systems. Furthermore PLA is applied to fibers for agricultural nets[16,17] and also into environmentally friendly golf tees.[18] It exists in the raceme *D,L* at various rates, usually at 50–50 ratio, and in the singles *D* and *L* separately.[19] PCL, despite being considered the ''minor'' within the polyester family, is gaining an increasing attention for applications in the biomedical and pharmaceutical fields, particularly for drug delivery systems, sutures and for scaffolds in the growing area of tissue engineering.[20] This is mainly due to its following characteristics[1,21,22]: (a) easy and cheap to be synthesized from ε-caprolactone; (b) its semicrystalline structure allows a very slow *in vivo* adsorbance and devices produced show good long lasting mechanical properties as they undergo nonenzymatic bulk hydrolysis; (c) the sole released metabolite is the very well tolerated ε-hydroxycaproic acid. Both such polymeric biomaterials surely play an essential role in tissue engineering,[8–12] one of the most innovative approach for tackling many diseases and body parts that need to be replaced, where they're applied for housing the cells and are usually shaped in two or three dimensional structures, the so-called scaffolds.[13]

Despite macroscopic effects of polymer degradation, kinetics and devices properties are well known and have been widely investigated,[2,23] not the same interest appears in relation to manufacturing topics.[2] As such polymers are mainly used in the fiber form; melt spinning and solvent casting are considered the main choices.[24] These methods are enhanced by the guarantee of low polymer degradation during process but sometimes the presence of residual solvent does not meet the strictest requirements for medical uses, such as for further manufacturing of scaffolds

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TABLE I
Physico-Chemical Properties of used Polymers (PLA and PCL) as Given by Respective Producers

Physico-chemical properties (given by producers)	Units	PLA	PCL
Mean molecular weight (M_w)[a]	Da	ca. 265,000	n.a.
Mean numerical molecular weight (M_n)[a]	Da	ca. 134,000	ca. 80,000
Residual monomer	%	<0.5	n.a.
Organic solvents	%	<0.1 (acetone)	n.a.
Heavy metals	PPM	<10	n.a.
Catalysts	PPM	<50 (tin)	n.a.
Water	%	<0.5	<0.5
Fusion temperature	°C	170–180	125
Aspect	–	Flakes	Granule
Color	–	White	Whitish
Odor	–	Odorless	Odourless

[a] M_w and M_n evaluations may be affected by an error in the range of 5%.

for tissue engineering applications or for pharmaceuticals applications such as drug delivery systems. Modern approaches have also been studied for fabrication of micro and nano drug delivery systems.[25,26] Despite the great technological achievements, such processes cannot undergo extensive and massive industrial scale productions where injection molding and extrusion indeed appear the only alternatives to melt spinning.[2,27–29] Both such processes carry the inner risk of degrading polymers[2,27–29] and thus leading to a remarkable reduction in mean molecular weight and a wider distribution, having as effects an important worsening of polymer mechanical characteristics and a reduction in degradation mean time. Alexis[2] well describes the controversial discussion related to this aspect that indeed sees major evidences leading to degrading effects of both technologies[28,29] than nondegrading ones.[27] Furthermore, degradation seems to occur also during the production of microspheres.[26] For sake of completeness it has to be said that a growing interest to thin film methods is coming up in recent years too.[30]

Seen that polymer degradation during manufacturing is a key factor to be kept under control, the aim of this work is to specifically test the efficiency of microextrusion evaluating the degradation of PLA and PCL after processing.

Microextrusion is a special production technology, far from being a simple scale down of traditional extrusion that is gaining wider diffusion in recent years for its numerous applications in different industrial fields.[4–7,31–34] Particularly, it represents an extremely valid alternative to nowadays used processes in the biomedical field for the productions of tubes, filaments or porous wires that can be composed in patches, scaffolds, and other two or three-dimensional shapes for tissue engineering applications. Furthermore microextrusion is also known to fit productions for resorbable implantable devices for orthopaedic surgery, from vertebral discs to fixation screws.[4–7] Within the pharmaceutical field, for its inner nature, microextrusion easily allows both filaments and tubes to be made porous or blended with other materials and even drugs, thus in this last case obtaining drug delivery systems and preparations.[31] On the other hand, for sake of completeness, microextrusion has been recently studied and applied also to special ceramic productions,[32–34] not only for biomedical applications.

Even if microextrusion is not a brand new technology to literature, as previously described and according to our knowledge, it has never undergone a specific study focused on assessing it as a suitable nondegradative process for manufacturing resorbable polyesters for biomedical and pharmaceutical applications.

METHODS

Raw materials

The choice of polymers for this study was driven by their potential applicability within pharmaceutical and biomedical industry. Thus we went for commercially available PLA and PCL, having high mean molecular weights and being used in medical and pharmaceutical applications:

PLA, Resomer® L207S, Poly-L-Lactide by Boeringher (Germany), M_w 265 KDa [CAS 33,135-50-1];
PCL, Poly-ε-CaproLactone by Aldrich (USA), M_n 80 KDa [CAS 24,980-41-4].

Main data is reported in Table I, where chemical–physical properties are reported as given by producers.

Experimental samples production

Once plant was set, materials were taken out of their sealed shipping packages and then processed. Proc-

essing temperatures were assessed by means of differential scanning calorimetry. Five random samples were taken from start batches and from extruded filaments on which assays were carried out.

PLA

As material arrived in flakes, before proper extrusion granulation has been applied by means of melting at 180°C and low pressure (12.5 MPa) extrusion followed by cooling down in air at room temperature (20°C) then dicing into granules of about $2 \times 2 \times 2$ mm^3.

Extrusion was done vertically with a three zones microextruder, using a special screw, a 6.6 mm die and a 4 mm pin, machines and tools all entirely engineered and supplied by Gimac, temperatures in the five extrusion zones were 100, 110, 120, 120, and 115°C.

PCL

As material is shipped in pellets shape, it can be directly extruded. Extrusion was done vertically with a three zones microextruder, using a special screw, a 6.6 mm die, and a 4 mm pin, machines and tools all entirely engineered and supplied by Gimac, temperatures in the five extrusion zones were 70, 80, 90, 90, and 75°C.

Obtained filament samples were cut in liquid nitrogen and then SEM (Evo 50 EP, Zeiss, Germany) images of sections were taken and are here reported, respectively: PLA microfilament in Figure 1 and PCL one in Figure 2.

Physical–chemical analysis

Mean molecular weight, molecular weights distribution, and inherent viscosity have been monitored.

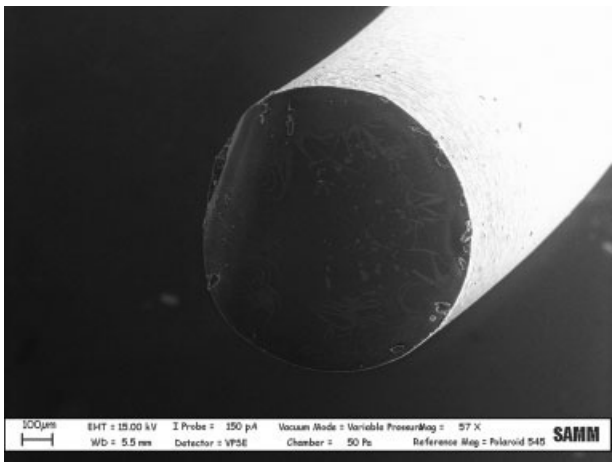

Figure 1 SEM image of PLA filament sample section (broken in liquid nitrogen).

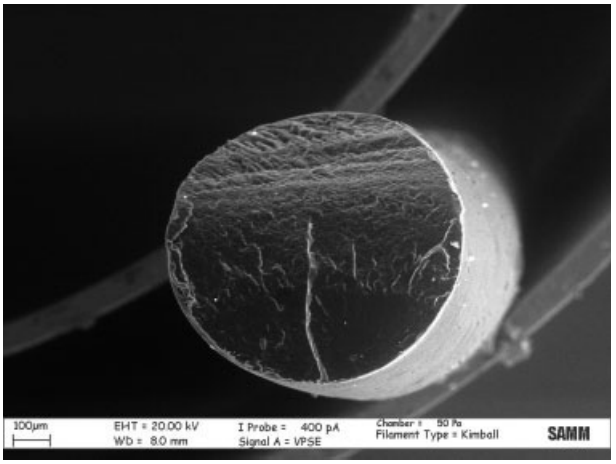

Figure 2 SEM image of PCL filament sample section (broken in liquid nitrogen).

GPC has been applied to evaluate molecular weight distributions:

eluent: TetraHydroFuran (THF, CAS nr. 109-99-9)

solvent: THF

chromatograph: Jasco, Waters Styragel columns HR3, HR4 and precolumn

calibration: Mark-Houwink method with standard mono-dispersed polystyrene (PS) and PLA (both from Polymer Standard Service GmbH, Germany) and standard PCL (Aldrich, USA)

sensor: refraction index, Jasco

Viscosity has been evaluated to obtain confirmation data:

viscometer: Viscotester VT5R (Haake, Rezzato, Italy)

solvent: CH_2Cl_2

temperature: +25°C

Samples keeping:

atmosphere: vacuum, dark sealing (away from direct light)

temperature: +4°C

For logistic reasons such keeping procedure has made necessary to avoid polymer degradation to initiate due to atmospheric moisture and be enhanced by exposing samples to room temperature and direct light.

RESULTS AND DISCUSSION

Molecular weight distributions of PLA have been assessed for the flakes as provided by producer, for the diced granules we obtained, and for the extruded filaments. On the other hand, for PCL, molecular weights have been assessed for the shipped pellets and for the extruded fibers. GPC analysis has been carried out on each of the five samples per each type of each polymer. Results are reported in Table II, where mean molecular weights (M_w), mean

TABLE II
Mean Molecular Weights (M_w) with Relative Standard Deviations (std), Mean Numerical Molecular Weights (M_n) with Relative Standard Deviations (std), and Dispersivity ($D = M_w/M_n$) Relating to PLA and PCL Before and After Processing

	M_w (Da)	std	M_n (Da)	std	D
PLA					
Flakes	269,000	8367	134,000	4183	2007
Granule	262,000	8573	130,000	5099	2015
Fiber	255,000	7906	126,000	4637	2024
PCL					
Granule	123,900	4002	81,000	2531	1530
Fiber	119,200	3773	77,000	2433	1548

numerical molecular weights (M_n), and dispersivity index ($D = M_w/M_n$) are presented. Data standard deviations are reported as well.

Viscosities[21] have been assessed on the flakes for PLA, on the pellets for PCL and on the extruded fibers for both polymers. Intrinsic viscosity data obtained are reported in Table III, together with relative standard deviations.

Mean molecular weight variations resulted very weak and within the order of 5% (M_w change), same as for molecular weight distribution variation, that resulted in the order of 6% (M_n change). Viscosities variations resulted in the order of 8.5 and 4.4%, respectively. Taking into account the instrumental tolerance (±5%), standard deviations (all in the range of about 3%) and batch to batch production differences we can affirm that the obtained data showed no significance in terms of molecular weights modifications, nor any correlation appears between data an eventual massive polymer bulk degradation.

Not only we proved confirmation of troubleless manufacturing of these polyesters with microextrudering technology, something that can be given for granted,[4–6] but physicochemical analysis showed neither a significative difference in the molecular weight distribution nor a significative reduction of the mean molecular weight between both PLA and PCL samples before and after extrusion. Viscosity evaluation proved support to the molecular weight analysis, indicating that an eventually occurred degradation might have resulted being nonsignificative. It has to be underlined that all data obtained remained within tolerances of analytical instruments.

Such results place themselves within the on-going debate[2] related to effects onto polymer molecular weights of various processing technologies: our results are indeed fully compatible and comparable with those from Rothen-Weinhold who reported[27] that the effect of extrusion of PLGA 75/25 and PLGA 50/50 at 90°C caused no significant decrease in M_w (range of 5%). But, as stated before, such a position is in contrast with those from Weiler and Gogolewski who reported[29] that PDLA 105–170°C standard extrusion of 280 KDa PLLA induced a 40% mean molecular weight loss as a result of thermo-oxidative degradation during processing. For seek of completeness and to set a new point in this still open discussion,[2] it has to be said that all cited experiments[27,29] have been carried out with standard extruders and not with microextruders, as we indeed did. According to our belief this is the main reason of the reported polymer degradation together with the high temperatures Weiler and Gogolewski[29] had to apply. Indeed, heading more deeply inside into traditional extrusion, critical aspects are the high thermal and mechanical stresses that the polymer has to face during the processing within the extruder screw and flow chamber and the high amount of time of resilience in such stressful conditions. On the other side, within a microextruder, material is processed at better conditions in terms of stable thermal, pressure, and flow gradients. Temperature, pressure, and stresses in general are kept at the lower required levels to permit processing but at same time minimize damaging effects to processed materials. Such features are achieved thanks to the low dead volume (a 12-mm microextruder has a dead volume smaller then 10 cm^3), to the accurate design and rheological dimensioning of screw and flow channels and to short processing times that altogether allow processed polymer not to undergo so high mechanical and thermal stresses to induce molecular weight degradation.

Thus, as explained, microextrusion technology is not a simple scaling down of common extrusion processes but it's a total revision of the melt pumping core technology, allowing the process to face and solve problems related to low dimension productions (easily down to few microns), small volumes, and low amount of raw materials processed (few grams per hour, independently from state: powders, pellets, gels or pastes), repeatability, constancy in production, process feasibility and last but not least the possibility of having GMP ready plants, with all the deriving positive consequences. At a whole glance, microextrusion shares extrusion advantages, but not disadvantages. Indeed microextrusion keeps

TABLE III
Assed Intrinsic Viscosities η (with Relative Standard Deviations (std)) for the Flakes for PLA and on Pellets for PCL and the Extruded Fibers of both Polymers

	PLA		PCL	
	η intrinsic (dL/g)	std	η intrinsic (dL/g)	std
Flakes	1.36	0.045	N.A.	N.A.
Granule	N.A.	N.A.	2.25	0.071
Fiber	1.24	0.041	2.15	0.068

into consideration not only macroscopic aspects—such as shape, dimensions, geometric ratio and cross section design—but also microscopic aspects such as crystallinity, molecular weight, inclusions, residual stresses, and surface roughness. Such a great sensitivity is achieved by controlling all process parameters, from physical–chemical ones to resilient times, from temperature gradients to local shear stress.

CONCLUSIONS

It can be thus concluded that the microextruding procedure we set out leaves substantially unmodified the molecular weight distributions of PLA and PCL, without producing any evident reductions in their respective mean molecular weights. The obtained data prove confirmation that the microextrusion procedure applied represents a proper and risk-free high molecular weight polymer processing solution for obtaining nondegraded fibers made of these resorbable polyesters. Furthermore, seen the wide range of applicable dies and heads to the used microextruders, the proposed method can be easily applied to the production of a huge variety of diameters, ranging from tens of microns to some millimeters and the possibility of working with small batches of raw materials and at low production rate makes of microextrusion a very good candidate for pharmaceutical and biomedical production lines where PLA, PCL and their blends are commonly used.

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