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Structured drug-loaded bioresorbable films for support structures

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Abstract—Bioresorbable films can serve simultaneously as anatomic support structures and as drug delivery platforms. In the present study, bioresorbable PLLA films containing dexamethasone were developed through solution processing. The effect of processing parameters on the film morphology and the resulting mechanical properties was studied. A model describing the structuring of these films is suggested. Generally, the solvent evaporation rate determines the kinetics of drug and polymer crystallization and thus, both the mode of drug dispersion in the polymer and the resulting mechanical properties. Two types of structured films were studied: (1) a polymer film with drug located on its surface, obtained due to drug skin formation accompanied by a later polymer core formation; and (2) a polymer film with small drug particles and crystals distributed within the bulk, obtained by parallel solidification of the two components. A prototypical application of these films is an expandable biodegradable support structure (stent), which we have developed. This stent demonstrated good initial mechanical properties. The film structure has only a minor effect on the stent radial compression strength, but more significantly affects the tensile mechanical properties.

Key words: Bioresorbable films; poly(lactic acid); stent; dexamethasone.

INTRODUCTION

Polylactic acid (PLA) is one of the most important biodegradable polymers, being used in a wide range of clinical applications, such as devices for orthopaedic
surgery [1–5], cardiovascular surgery [6, 7], sutures [8], and as drug delivering implants [9–12].

The semi-crystalline poly(l-lactic acid) (PLLA) is well known for the first three mentioned applications, where high mechanical strength and toughness are required. This polymer can be formed into films, tubes and matrices using standard processing techniques such as molding, extrusion, solvent casting and spinning [8].

The most popular types of drug delivery systems based on PLLA are microparticles, implants and fibers [9]. Various melt processing techniques, such as compression molding, injection molding and extrusion have been utilized to fabricate PLLA based implants loaded with bioactive agents. However, the limiting factor in case of melt processing of implants for drug delivery is the heat stability of the active agent [9]. Solution casting of polymers is a well known method for preparation of PLA-based films. In order to incorporate drugs by this method, the polymer is dissolved in a solvent and mixed with the drug, prior to casting. Dexamethasone is a steroidal anti-inflammatory drug. It has been incorporated into biodegradable polymer microparticles for various uses [13–15]. In the current research PLA films loaded with dexamethasone were developed through solution processing. Polymer/dexamethasone films are reported in this paper for the first time.

The currently-used metal stents support blood vessels, airway and other structures, but require a removal operation and do not provide drug delivery [16–18]. A biodegradable stent that would support such conduits as the neonatal trachea, until the airway matures thereafter being totally resorbed, would be ideal. We developed a novel expandable PLLA based stent, prepared from a solution-cast PLLA based film. Dexamethasone is incorporated into this film based stent to permit its controlled local release. In addition to its anti-inflammatory activity, dexamethasone has been demonstrated to inhibit fibrotic response. Therefore the addition of this drug may be helpful in the prevention of proliferative reactions, such as an induced stenosis.

The current research focuses on the effects of film processing parameters on the morphology and the resulting mechanical properties of the films. In addition, a model describing the structuring of these films is suggested. The basic mechanical properties of stents, prepared in this fashion are described.

**EXPERIMENTAL**

**Materials**

Bioresorbable polymers were: high molecular weight poly(l-lactide) (H-PLLA), Resomer L21 (i.v. = 3.6 dl g\(^{-1}\) in CHCl\(_3\) @ 30\(^\circ\)C), Boehringer Ingelheim, Germany; low molecular weight poly(l-lactide) (L-PLLA), L-PLA (i.v. = 1.02 dl g\(^{-1}\) in CHCl\(_3\) @ 30\(^\circ\)C), Birmingham Polymers, USA; and poly(DL-lactide) (PDLLA), DL-PLA (i.v. = 1.07 dl g\(^{-1}\) in CHCl\(_3\) @ 30\(^\circ\)C) Birmingham Polymers, USA.
Non-inflammatory drugs were: Dexamethasone (DM) USP, 9α-fluoro-162-methylprednisolone, Sigma D-9184; Hydrocortisone, 11,17,21-trihydroxypregn-4-ene-3,20-dione, Calbiochem 3867; and Curcumin, 1,7-bis[4-hydroxy-3-methoxy-phenyl]-1,6-heptadiene-3,5-dione, Sigma C-1386.

**Film preparation**

Polymer films (0.12–0.15 mm thickness) consisting of poly lactic acid and dexamethasone were prepared by a three step solution processing method:

(a) Components were mixed in chloroform at room temperature until polymer dissolution. A constant (polymer + drug) quantity was chosen for all experiments. In most experiments DM content was 2 wt%. In others, contents of 3, 5, and 10 wt% were used. For each polymer/drug composition two kinds of solution were prepared, diluted and concentrated. The solubility of DM in chloroform at room temperature is approximately 1 mg ml$^{-1}$.

**Dilute solution.** A dilute solution was prepared by using a relatively large volume of chloroform (concentration range of the polymer: 0.01–0.02 g ml$^{-1}$; concentration range of DM: $2 \times 10^{-4}–10^{-3}$ g ml$^{-1}$). Both DM and poly lactic acid were totally dissolved.

**Concentrated solution.** A concentrated solution was prepared by using a relatively small volume of chloroform (concentration range of the polymer: 0.05–0.1 g ml$^{-1}$; concentration range of DM: $10^{-3}–5 \times 10^{-3}$ g ml$^{-1}$). In this solution the polymer was totally dissolved, while the DM powder was only broken into small particles (aggregates), which yielded an opaque solution.

(b) Solution casting into a Petri dish and solvent drying under atmospheric pressure at room temperature. Two solvent evaporation rates were used: a relatively slow rate of 2–5 ml h$^{-1}$ and a relatively fast rate of 10–20 ml h$^{-1}$.

(c) Isothermal heat treatment at 90°C for 1 h in a vacuum oven.

**Morphological characterization**

**Films.** Polarized light microscopy (LM) was performed using an Olympus BHS compound microscope and a Nikon Diathot inverted light microscope. Transmission electron microscopy (TEM) of ultramicrotomed samples was performed using a Jeol 1200 EX II at an accelerating voltage of 80 kV. High-resolution scanning electron microscopy (HRSEM) of cryogenically fractured surfaces was performed using a Leo Gemini-982, at an accelerating voltage of 1 kV.

**Dexamethasone powder.** Scanning electron microscopy (SEM) was performed for the drug powders, using a Jeol JSM 840 A at an accelerating voltage of 10 kV. The SEM samples were gold-sputtered prior to observation.
Thermal analysis

Melting temperature \( (T_m) \), heat of fusion \( (\Delta H_m) \), and degree of crystallinity \( (% C) \) were determined by differential thermal analysis using an indium calibrated TA Instruments DSC 2010 differential scanning calorimeter (DSC). The measurements were carried out on 10 mg samples under \( \text{N}_2 \) atmosphere, heating the samples from 30 to 250°C (above their melting points). The analysis was performed with a TA Universal Analysis software. The degree of crystallinity, \( % C \), was calculated by the following relationship:

\[
% C = \frac{\Delta H_m}{\Delta H_F} \times 100,
\]

where \( \Delta H_m \) and \( \Delta H_F \) are the heats of fusion of the sample (a semicrystalline material) and the perfect crystal, respectively. For PLLA \( \Delta H_F = 93.6 \text{ J g}^{-1} \) [19].

Mechanical properties measurements

The mechanical properties of the films were measured at room temperature in unidirectional tension at a rate of 10 mm min\(^{-1}\) (ASTM D 882-97), using a Universal Testing System machine, MTS Systems Corporation, Eden Prairie, MN, USA.

The radial compression strength of the stents was measured by a special chamber, constructed in our laboratory. This chamber permits hydrostatic pressure to be applied to the external surface of the stent. The chamber was ported to a manual air pump for pressurization and a sphygmomanometer was used to measure the pressure in the chamber. The pressure difference across the stent wall was increased gradually and the resulting change in the stent diameter was measured. Five samples were tested for each point, for both mechanical property measurements.

RESULTS AND DISCUSSION

The morphology of PLA/dexamethasone films

The film structures created from the diluted and concentrated solutions are termed as ‘A’ and ‘B’, respectively. Figure 1 presents polarized LM observations of L-PLLA/DM(A), L-PLLA/DM(B), H-PLLA/DM(A), and H-PLLA/DM(B) films containing 2 wt% DM and treated at 90°C, compared with the corresponding neat matrix films, L-PLLA and H-PLLA. The melting points of these films and their degree of crystallinity are presented in Table 1. Large spherulites (50–100 \( \mu \text{m} \)) are observed for the L-PLLA film, as can be expected for a highly crystalline polymer (53.6 \%C). The H-PLLA film is less crystalline than the L-PLLA one (41.4 \%C) and its spherulites are relatively small (less than 10 \( \mu \text{m} \)). The structure and crystallinity differences of these polymers result mainly from the molecular weight difference. While the relatively short L-PLLA chains (i.v. \( = 1.0 \text{ dl g}^{-1} \), corresponding to approximately 130 kD) are likely to crystallize, the long H-PLLA
chains (i.v. = 3.6 dl g$^{-1}$, corresponding to approximately 380 kD) is more difficult for crystallization. The melting temperature of the H-PLLA film is higher than that of L-PLLA, probably due to the existence of ‘larger’, i.e. more ‘perfect’ crystals. It should be mentioned that in order to observe the H-PLLA structure, a different degree of polarization was used, and as a result the H-PLLA films appear with a dark background.

Large rectangular DM crystals (50–300 µm) are observed on the surface of both PLLA(A) films. These crystals can be observed without a polarizer. In both cases, the structure of the polymer film (below the DM crystals) is similar to that of the neat matrix polymer, indicating that separate crystallization processes probably occur for PLLA and DM at different drying stages. Each DM crystal is actually composed of smaller crystals, gathered during an advanced crystallization stage. As can be expected for such morphologies, the degree of crystallinity of the A type containing DM PLLA films (52.2 %C for L-PLLA/DM(A)) and 38.2 %C

Figure 1. Polarized light micrographs of PLLA based films.
Table 1.
Melting temperature and degree of crystallinity of PLLA-based films

<table>
<thead>
<tr>
<th>Film</th>
<th>Melting temperature (°C)</th>
<th>Degree of crystallinity (%c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-PLLA</td>
<td>174</td>
<td>53.6</td>
</tr>
<tr>
<td>L-PLLA/DM(A)</td>
<td>173</td>
<td>52.2</td>
</tr>
<tr>
<td>L-PLLA/DM(B)</td>
<td>174</td>
<td>52.0</td>
</tr>
<tr>
<td>H-PLLA</td>
<td>181</td>
<td>41.4</td>
</tr>
<tr>
<td>H-PLLA/DM(A)</td>
<td>181</td>
<td>38.2</td>
</tr>
<tr>
<td>H-PLLA/DM(B)</td>
<td>181</td>
<td>37.5</td>
</tr>
</tbody>
</table>

for H-PLLA/DM(A) are very similar to those of the neat PLLA films (53.6 %C for L-PLLA and 41.4 %C for H-PLLA).

LM observations of B type PLLA/DM films show a difference in structure, compared to that of the neat matrix polymers. Most of the DM is located within the PLLA film and only a small part (less than 10%) is located on the surface. Although a polarizer was used, the polymer characteristic features within the L-PLLA/DM(B) film almost cannot be observed, probably due to distribution of the drug within the polymer film, disturbing the birefringence effects. Since the degree of crystallinity of this film is also high (52.0 %C) and similar to that of the neat L-PLLA (53.6 %C), it can be assumed that the L-PLLA film is also arranged in a spherulitic structure. However, the spherulites of the PLLA within the L-PLLA/DM(B) film are probably smaller that those of the neat L-PLLA film. A similar morphology, where most of the DM is dispersed within the polymer matrix, is observed also for the H-PLLA/DM(B) film. In this case the polymer structure can be observed, due to the relatively high degree of polarization. It appears that the spherulites of the PLLA within the H-PLLA/DM(B) film are similar to those building the neat H-PLLA film. The next chapter will elucidate that in order to incorporate the drug in the polymer film, the two components should crystallize in parallel. Interestingly, for both PLLA's the melting temperature is not affected by DM incorporation in the film (Table 1), indicating that the DM does not affect the PLLA crystal’s ‘size’.

Similar morphologies were observed for the corresponding films containing 3, 5, and 10 wt% DM within the PLLA matrix. In order to better understand the effect of the matrix polymer structure on the DM distribution, PDLLA based films were prepared. The two basic types of solutions, diluted and concentrated, yielded the A and B film types, respectively, as shown in Fig. 2. The PDLLA matrix is amorphous and therefore does not show any typical structure. These morphology studies suggest that the DM mode of dispersion depends mainly on the starting solution and derived parameters (to be discussed below). In the content of this study, the type of poly-lactide affects the polymer morphology, but has a minor effect on the drug distribution in it. The chemical structure of DM is different than that of PLLA and therefore, for the B type films based on semicrystalline matrix, most of the DM is probably located around the PLLA spherulites, in amorphous domains. For the B type films based on semicrystalline matrix, the DM crystals are located
within the amorphous regions of a semicrystalline polymer, around the spherulites. A finer DM dispersion is obtained within the amorphous PDLLA matrix, due to absence of crystalline structure features, i.e. the DM is not ‘directed’ to certain domains within the matrix polymer.
Structuring of solution-cast PLA/drug films

As previously shown, two extreme structures were created: (a) a polymer film with large DM crystals located on its surface; and (b) a polymer film with small drug crystals and particles located within the bulk. The process of film creation during solvent drying was studied to elucidate the structures created and to understand how the various processing parameters affect the film morphology. Inverted LM micrographs of various points during A and B L-PLLA/DM film formation are presented in Figs 3 and 4, respectively. The polymer crystallization process could

Figure 3. Inverted light micrographs showing the process of PLLA/DM(A) film formation.
not be observed via inverted LM, and therefore, polarized compound LM was used to complete the study. The A type PLLA/DM film formation process is as follows:

(a) Nucleation of DM particles on the solution surface (Fig. 3a). Since the highest rate of solvent evaporation is obtained near the solution/air interface, the primary drug nucleation occurs there. In this stage the solution is diluted.

(b) The concentration of the nuclei increases in parallel to their growth. Hence, many 1–10 μm particles and aggregates are observed (Fig. 3b). The polymer solution is less diluted in this stage.

Figure 4. Inverted light micrographs showing the process of PLLA/DM(B) film formation.
(c) The DM particles segregate, due to inter-particle interactions and crystallization of selected sites, to form ordered shapes (Fig. 3c). The polymer solution is relatively viscous, since most of the solvent has already been evaporated.

(d) The DM particles are merged to form large rectangular and hexagonal crystals (Fig. 3d). A spherulitic structure is observed beneath, within the gel-like solution. PLLA crystallization probably started during stage c, at least near the surface where the solvent evaporation rate is relatively high. However, lamellae or very small spherulites cannot be observed via polarized LM, due to lack of birefringence effects. Therefore, the polymer structure was not observed before stage d.

(e) Final drug crystals of characteristic dimensions of 50–300 μm are obtained.

The B type PLLA/DM film formation process is as follows:

(a) Nucleation of DM particles in a very viscous solution and also on its surface. The L-PLLTA starts its crystallization (Fig. 4a).

(b) The DM particles grow, in parallel to the polymer crystallization. Many 1–10 μm particles are observed (Fig. 4b).

(c) Segregation of DM particles within the viscous medium of the crystallizing polymer (Fig. 4c). The PLLA spherulites are relatively big and the DM particles migrate to the amorphous domains, around the spherulites and tend to accumulate there.

(d) A semi-network of DM crystals is created in the amorphous domains of the semi-crystalline PLLA matrix (Fig. 4d1). A higher magnification (Fig. 4d2) indeed shows the rounded shape ‘spherulitic features’ of the matrix polymer.

Hence, it is suggested that in order to obtain an A type polymer/drug film, where the drug is located on the surface of the polymer, both components need to be fully dissolved in a common solvent. A relatively low molecular weight drug tends to crystallize before the high molecular weight polymer. Therefore, during a slow evaporation process, drug nucleation occurs on the surface of the solution, where the highest drying rate is obtained. This stage is accompanied by diffusion of DM molecules from the solution to its surface and skin formation. A later polymer core formation occurs in parallel, to further drug particle merging and crystallization on its surface. In contrast, in order to obtain a B type polymer/drug film, where the drug is distributed within the polymer, a relatively concentrated solution must be used, i.e. the polymer solution contains fine drug particles not totally dissolved. Thus, there is over saturation of drug within the solution. After casting, parallel crystallization of both drug and polymer occurs, due to the relatively rapid drying. Since the nature of the drug is different than that of the matrix polymer, the drug particles migrate to the amorphous domains of the crystallizing polymer, where they segregate to form a semi-network structure within the matrix polymer. The concentrated solution contains DM particles rather than molecules, which diffuse more slowly. Therefore, a DM core formation is not favored.
In order to further examine the effect of solvent evaporation rate on the film morphology, a diluted L-PLLA/DM solution was cast and dried relatively rapidly. Drug nuclei appeared on the solution surface, but most of the DM crystallization occurred in a gel-like concentrated solution. As a result, a structure similar to that of the B type film was created. It is thus suggested that the kinetics of solution drying plays a major role in the DM mode of dispersion in a polymer film. The opposite process of starting with a concentrated solution and obtain an A type morphology does not occur, even when the drying rate is extremely slow. The relatively slow diffusion rate of DM particles in a viscous medium probably does not enable drug crystal formation on the surface of a growing polymer film.

The net effect of DM re-crystallization on morphology was investigated at dilute and concentrated solution conditions, observing the obtained structure by SEM. The as-received DM powder consists of particles of 0.1–3 μm, partially aggregated (Fig. 5a, b). Re-crystallization of DM from dilute solution leads to formation of large rectangular crystals (Fig. 5c). It appears that these crystals are composed of well packed, small primary particles, similar to those of the as-received powder. These tend to merge to large, well arranged structures, due to the slow drying process. It is thus suggested that the rectangular shapes are probably a tertiary
structure. In contrast, re-crystallization of DM from concentrated over-saturated DM solution, leads to formation of a structure similar to the original one. Hence, these SEM observations show that the DM distribution within a PLLA film is determined mainly by the kinetics of drug re-crystallization, whereas the polymer chain structure and morphology have a minor effect on the DM distribution. The latter have a significant effect on the film properties.

LM observations of the films enable one to elucidate the film structure. However, a better view of DM dispersion within the B type film and its particles size could not be observed via LM. Therefore, the morphology of these films was also studied by electron microscopy. TEM and HRSEM micrographs of H-PLLA/DM(B) film are presented in Fig. 6. DM in the form of small rectangular shapes (1–5 μm) appear in addition to small particles (less than 1 μm), within the whole cross section area of the film (Fig. 6a). This indicates the partial formation of the DM tertiary structure, in spite of the relatively fast drying. The features of the spherulitic PLLA cannot be observed, due to their low contrast. HRSEM micrograph of the cryogenically fractured surface of the film indicates a poor PLLA-DM interphase adhesion. The chemical nature of the DM is aromatic while that of the PLLA is aliphatic. Therefore, the PLLA does not tend to ‘wet’ DM, resulting in poor polymer/drug interphase. The PLLA contains ester groups and each DM molecule contains two carbonyl and three hydroxyl groups. Therefore, specific strong interactions, namely hydrogen bonds, could have been formed between the carbonyl oxygens in the PLLA chains and the hydroxyl hydrogens in the DM. However, in this system since DM contains both groups, carbonyls and hydroxyls, these strong intermolecular interactions are probably created between adjacent DM molecules and particles, leading to strong DM segregation during film drying.

To conclude this part, both kinetic parameters of film formation process and thermodynamic parameters of the system’s components affect the film morphology. The rate of solvent evaporation and the resulting rate of drug and polymer crystallization have a significant effect on the drug distribution and its structure. Solubility effects
of the system components determine the nature of the starting solution and therefore affect diffusion processes during drying. Interestingly, PLLA/hydrocortisone and PLLA/curcumin films, prepared from dilute and concentrated solutions, also showed the A and B structures, respectively. This indicates that the methods of structuring demonstrated in this research, are general.

**Mechanical properties in tension**

Stress–strain curves of H-PLLA and L-PLLA based films are presented in Fig. 7. The measured maximal tensile strength (at break), elastic modulus and maximal strain (at break) are presented in Table 2. It should be noticed that the treated films are relatively brittle and their tensile failure occurs at or slightly beyond the yield stress. Therefore the yield stresses and strains are very similar to the maximal stresses and strains, respectively. The untreated as-cast PLLA films are ductile and have relatively low strength and stiffness (Fig. 7a). Heat treatment at $T > T_g$ results in increase in strength, stiffness and brittleness. One of our studies [20] showed that this occurs due to further crystallization and evaporation of solvent residues. The mechanical properties of a polymer/drug film are determined by the film composition, the polymer’s chain structure and its morphology and the drug distribution. The neat H-PLLA is stronger and tougher than L-PLLA, probably due to the higher molecular weight. It should be recalled that the L-PLLA treated film exhibits 53.6 %C, while the H-PLLA treated film is less crystalline (41.4 %C, Table 1). Hence, the crystallinity effect is not strong enough to compensate for the molecular weight effect; as a result, the more crystalline L-PLLA is weaker than the less crystalline H-PLLA. The chance of brittle failure is decreased by raising molecular weight, which increases brittle strength, and reduces degree of crystallinity [21]. Therefore, in addition to their better strength and stiffness, the H-PLLA films are more ductile than the L-PLLA. Also, polymers with smaller, finer-textured spherulites tend to fail at relatively high strains, while those with large, coarse spherulites often fail by brittle fracture between spherulites at low strains. Hence, the better ductility of the H-PLLA is obtained due to differences in molecular weight, %C, and the polymer texture.

In general, incorporation of DM to H-PLLA or L-PLLA decreases the strength, modulus and maximal strain (Fig. 7b, c and Table 2). As previously mentioned, the treated PLLA is relatively brittle and its tensile failure occurs at or slightly beyond the yield stress. The change in ductility due to addition of the drug is not significant. However, it seems that in the B type films, failure occur below the yield point. In the A type films, the DM is located on the surface of the PLLA matrix, the polymer structure is very similar to that of the neat PLLA and therefore, the changes in mechanical properties are relatively small. The poor quality of the layers close to the PLLA-DM interphase is probably responsible to these changes. In contrast, in the B type films, the DM is located within PLLA. As a result, for both, H-PLLA and L-PLLA, the deterioration of mechanical properties due to DM incorporation is more significant than in A type film. The DM molecules consist
Figure 7. Stress–strain curves of: (a) treated and untreated H-PLLA film; (b) treated H-PLLA based films; and (c) treated L-PLLA based films.
of a four-ring planar structure and therefore, could be expected to function as a stiff organic filler, increasing stiffness and strength. However, the totally different nature of these components, and the lack of interactions between them, contribute to a poor interphase adhesion and results in deterioration in mechanical properties. Interestingly, deterioration of mechanical properties due to drug incorporation is more significant for L-PLLA film than for the H-PLLA one, especially in the B type films (Table 2). It is thus suggested, that the relatively large amount of amorphous phase and fine spherulitic structure of H-PLLA can better tolerate drug incorporation than the smaller amount of amorphous phase and coarser structure of L-PLLA. Morphological studies of the treated films containing DM did not show any structural changes after applying tensile stress. This results from the low strains at break of the relatively brittle treated films (Fig. 7b, c).

**Expandable stents prepared from PLLA-based films**

Tubular stents developed of these films were investigated. Their radial compression properties are presented in Table 3. The maximal applied pressure using our radial compression chamber is 200 kPa, therefore higher strength values could not be measured. In general, the H-PLLA based stents are stronger than the L-PLLA base ones. They can endure a radial compression pressure of at least 200 kPa without exhibiting any deformation. The L-PLLA stents start to deform at 138 kPa and they break at 158 kPa. They exhibit a small elastic deformation before showing a brittle failure. Incorporation of DM in the film results in reduction in the stent’s radial compression strength and it starts to deform at lower pressure. However, both stent types, H-PLLA and L-PLLA can serve as conduit support structures (stents etc.), since their initial radial compression strengths are at least fifty times higher than the required values. The tensile mechanical properties of a polymer are more sensitive to poor polymer-filler interphase adhesion than compression properties. Therefore the stent’s compression strength can better tolerate drug incorporation than the tensile mechanical properties of the film.

The H-PLLA based film is stronger and more ductile than the L-PLLA film. It can better accommodate drug incorporation on the film surface and also in bulk.

### Table 2.
The mechanical properties in tension of PLLA-based films

<table>
<thead>
<tr>
<th>Film</th>
<th>Tensile strength (MPa)</th>
<th>Modulus (MPa)</th>
<th>Strain (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-PLLA (untreated)</td>
<td>22.6</td>
<td>453</td>
<td>142</td>
</tr>
<tr>
<td>H-PLLA</td>
<td>59.0</td>
<td>1250</td>
<td>5.4</td>
</tr>
<tr>
<td>H-PLLA/DM(A)</td>
<td>48.0</td>
<td>1182</td>
<td>5.4</td>
</tr>
<tr>
<td>H-PLLA/DM(B)</td>
<td>42.7</td>
<td>1165</td>
<td>3.7</td>
</tr>
<tr>
<td>L-PLLA (untreated)</td>
<td>19.0</td>
<td>255</td>
<td>107</td>
</tr>
<tr>
<td>L-PLLA</td>
<td>46.4</td>
<td>1222</td>
<td>4.2</td>
</tr>
<tr>
<td>L-PLLA/DM(A)</td>
<td>34.3</td>
<td>936</td>
<td>3.7</td>
</tr>
<tr>
<td>L-PLLA/DM(B)</td>
<td>17.3</td>
<td>870</td>
<td>2.6</td>
</tr>
<tr>
<td>Film type</td>
<td>Strength (kPa)</td>
<td>Initial deformation pressure (kPa)</td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>----------------</td>
<td>----------------------------------</td>
<td></td>
</tr>
<tr>
<td>H-PLLA</td>
<td>&gt;200</td>
<td>&gt;200</td>
<td></td>
</tr>
<tr>
<td>H-PLLA/DM(A)</td>
<td>&gt;200</td>
<td>&gt;200</td>
<td></td>
</tr>
<tr>
<td>H-PLLA/DM(B)</td>
<td>&gt;200</td>
<td>&gt;200</td>
<td></td>
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<tr>
<td>L-PLLA</td>
<td>158</td>
<td>138</td>
<td></td>
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<tr>
<td>L-PLLA/DM(A)</td>
<td>145</td>
<td>131</td>
<td></td>
</tr>
<tr>
<td>L-PLLA/DM(B)</td>
<td>138</td>
<td>117</td>
<td></td>
</tr>
</tbody>
</table>

In addition, the mechanical properties of the H-PLLA based stents are better than those of the L-PLLA based ones. Therefore H-PLLA stents are more applicable for supporting various body conduits and were chosen for further studies. After serving for a certain period of time *in vivo*, they will partially degrade and probably show lower mechanical properties, similar to the initial mechanical properties of the L-PLLA stents.

As mentioned before, biodegradable films can serve simultaneously as anatomic support structures and as drug delivery platforms. One of our recently reported studies is an *in vitro* study of these PLLA/dexamethasone films and the support devices (stents) prepared from these films [20]. It focuses on the mechanical properties of the films and the stents. The morphology, degradation and erosion processes and the polymer's initial molecular weight have significant effects on the resulting properties. The DM release from these films has also been studied. In general, during exposure to an aqueous solution a linear accumulative DM release profile was obtained for the A type films, throughout the 24 weeks of study. The B type films showed a linear accumulative release of DM for 12 weeks and then the rate of release decreased gradually with time. The DM release from the A type film was faster than that from the B type film. The release kinetics and a mathematical model describing the effects of diffusion and degradation processes will be reported in a separate manuscript.

**SUMMARY AND CONCLUSIONS**

Bioresorbable PLLA films containing Dexamethasone were prepared through solution processing accompanied by a post-preparation isothermal heat treatment. The effect of film processing parameters and components on its morphology and mechanical properties was studied. A model describing the structuring of these films was suggested.

The solvent evaporation rate determines the kinetics of drug and polymer crystallization and thus, the drug mode of dispersion in the film. The polymer chain structure and its morphology has a minor effect on the drug distribution. Solubility effects in the starting solution affect the post-casting diffusion processes, occuring in parallel to the drying step.
In general, two film structures were obtained: (a) A polymer film with large drug tertiary shapes located on its surface. This structure, derived from diluted solution, was obtained due to prior drug nucleation and growth on the polymer solution surface. This skin formation is accompanied by a later polymer core formation. (b) A polymer film with small drug particles and crystals distributed within the bulk. This structure, derived from concentrated solution, is obtained due to drug nucleation and segregation within a dense polymer solution. Solidification of drug and polymer occurred in parallel. The drug is located in amorphous domains of a semicrystalline matrix, around the spherulites.

The mechanical properties of the PLLA film are determined by the polymer's molecular weight, morphological features and the post-preparation heat treatment. Incorporation of drug in the PLLA film decreases its strength, modulus and ductility. The mechanical properties deterioration due to drug incorporation is more significant for the B type films than for the A ones. The former contains larger, poor polymer-drug interphase area. H-PLLA can better tolerate drug incorporation than L-PLLA, due to its lower degree of crystallinity and finer spherulitic texture.

Support structures (stents) developed from these films demonstrated good mechanical properties. The stent radial compression strength is determined mainly by the polymer structure. Drug incorporation has a minor effect on the stent's strength.

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REFERENCES