Paclitaxel-loaded composite fibers: Microstructure and emulsion stability

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Abstract: New core/shell fiber structures loaded with paclitaxel were developed and studied. These composite fibers are ideal for forming thin, delicate, biomedically important structures for various applications. Possible applications include fiber-based endovascular stents that mechanically support blood vessels while delivering drugs for preventing restenosis directly to the blood vessel wall, or drug delivery systems for cancer treatment. The core/shell fiber structures were formed by “coating” nylon fibers with porous paclitaxel-containing poly(DL-lactic-co-glycolic acid) structures. Shell preparation (“coating”) was performed by freeze-drying water in oil emulsions. The present study focused on the effects of the emulsion’s formulation (composition) and processing conditions on the porous shell structure, which actually reflects the emulsion’s stability and also the drug release profile from the fibers. In general, extremely porous “shell” structures were obtained with good adhesion to the core fiber. An increase in the emulsion’s drug content and copolymer composition demonstrated a significant effect on pore size and distribution, because of enhanced emulsion instability, whereas the homogenization rate and duration had only a slight effect on the pores’ microstructure. The thermodynamic parameters in the studied system are thus more important than the kinetic parameters in determining the emulsion’s stability and the shell’s porous structure. © 2006 Wiley Periodicals, Inc. J Biomed Mater Res 81A: 427–436, 2007

Key words: paclitaxel; composite fibers; controlled drug release; poly(DL-lactic-co-glycolic acid); porous structure

INTRODUCTION

Organ or tissue failure or loss is one of the most frequent and devastating problems in human healthcare. Principles of biomaterials, engineering, and biology are applied to the development and study of implantable medical devices or substitutes for damaged tissues. These may be based on fiber structures and may contain bioactive molecules that enhance the healing of the surrounding tissues or help cure certain diseases.

Few controlled-release fiber systems based on polymers have been investigated to date. The two basic types of drug-loaded fibers that have been reported are monolithic fibers and reservoir fibers. In systems that use monolithic fibers, the drug is dissolved or dispersed throughout the polymer fiber. For example, curcumin, paclitaxel, and dexamethasone have been melt-spun with poly(l-lactic acid) (PLLA) to generate drug-loaded fibers and aqueous drugs have been so-

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lution-spun with PLLA. Various steroid-loaded fiber systems have demonstrated the expected first-order release kinetics. In systems that use hollow reservoir fibers, drugs such as dexamethasone and methotrexate have been added to the internal section of the fiber. The advantages of drug-loaded fibers include ease of fabrication, high surface area for controlled release, and localized delivery of bioactive agents to their target. Disadvantages include poor mechanical properties due to drug incorporation and limitations in drug loading. Furthermore, many drugs and all proteins do not tolerate melt processing and organic solvents.

In one of our recent studies, we presented a new concept of core/shell fiber structures which successfully met these challenges. These composite fibers combine a dense polymer core fiber and a protein-loaded porous shell structure, that is, the drug or protein is located in a separate compartment (a “shell”) around a melt-spun “core” fiber. The shell is prepared using mild processing conditions. A schematic representation of the composite fiber structure is presented in Figure 1(a). This results in good mechanical properties as well as the desired drug release profile. Our new fibers are ideal for forming thin, delicate, biomedically important structures for various applications, such as fiber-based endovascular stents that mechanically support blood vessels while delivering drugs for prevent-
ing restenosis directly to the blood vessel wall, or drug delivery systems for cancer treatment. Paclitaxel is a potent cell proliferation inhibitor and is known to be very effective in the treatment of cancer as well as in preventing restenosis.\textsuperscript{11,12} It is highly hydrophobic, and its release from polymeric devices in an aqueous medium is therefore relatively slow.\textsuperscript{12} Porous structures that encapsulate the drug, such as our fiber’s shell, may therefore be beneficial in such cases.

Emulsions are metastable colloids made of two immiscible fluids, one being dispersed in the other in the presence of surface-active agents (surfactants).\textsuperscript{13} Inverted emulsions are composed of water droplets dispersed in a continuous oil (organic) phase. Emulsions are obtained by shearing two immiscible fluids, leading to the fragmentation of one phase into the other. They are metastable, and their life-time may vary considerably depending on the temperature and their composition. The instability is due to the large interfacial area, and therefore a large surface energy which is associated with finely dispersed systems.\textsuperscript{14} The stability of emulsions is highly important for their use as drug delivery systems. Separating a two-phase system produces a large surface area per drop, leading to a high excess Gibbs energy per drop, and thus to a tendency in the direction of decreasing the Gibbs energy.\textsuperscript{13,14} The destabilization of a two-phase emulsion goes through several consecutive and parallel steps before reaching the final stage of separated layers. Several types of interaction patterns may arise when two particles driven by random Brownian motion approach each other, including flocculation, coalescence, Ostwald ripening, and creaming.\textsuperscript{13,15,16}

The present study focuses on composite core/shell fiber structures loaded with paclitaxel. The porous shell (drug-containing section) was prepared using the technique of freeze drying an inverted emulsion. The effects of the emulsion’s formulation (components) and processing conditions on the shell’s microstructure were examined. The shell’s porous structure is important, since it may affect the drug release profile. It is also a good measure of the emulsion’s stability. Furthermore, these poly(\(\alpha\)-lactic-co-glycolic acid (PDLGA)-based inverted, freeze-dried emulsions are unique and can be loaded with many bioactive agents and may serve in a wide variety of biomedical and tissue regeneration applications.

**MATERIALS AND METHODS**

**Materials**

Ethilon\textsuperscript{TM} monofilament nylon sutures (model W597), Ethicon, USA, were used as core fibers. Biodegradable porous structures (the shell coating) were made of 75/25 poly(\(\alpha\)-lactic-co-glycolic acid) (PDLGA), inherent viscosity (i.v.) = 0.65 dL/g (in CHCl\textsubscript{3} at 30°C, ~97,100 g/mole), Absorbable Polymer Technologies, USA. Paclitaxel (Genexol\textsuperscript{TM}) was purchased from Sam Yang Corp., Seoul, Korea. Surface active agents

1. Pluronic L121\textsuperscript{TM}, a triblock copolymer of ethylene oxide and propylene oxide, with a mean molecular
weight of ~4400 Da was received as a gift from BASF, USA.
2. Poly(vinyl alcohol) (PVA), 87–89% hydrolyzed, molecular weight = 13,000–23,000 Da was purchased from Sigma.

Preparation of core/shell fiber structures

Fiber surface treatment

The sutures were surface-treated in order to dispose of the original fiber’s coating and to enhance the adhesion between the core fiber and the coating. The nylon fibers were slightly stretched on special holders and dipped in a 75/25 v/v formic acid/ethanol solution for 15 s. The fibers were then washed and dried in a vacuum oven at 65°C for 80 min.

Emulsion formation

A known amount of PDLGA was dissolved in chloroform to form an organic solution, and paclitaxel was added to the solution. Double-distilled water was then poured into the organic phase (in a test tube) and homogenization of the emulsion was performed using a hand-held homogenizer (OMNI TH, 7-mm rotor) operating at 16,500 rpm (medium rate) for 3 min, for most investigated samples. In order to investigate the effect of processing conditions on the porous shell structure, certain samples were prepared using homogenization rates of 5500 rpm (low rate) or 25,000 rpm (high rate), and homogenization durations of 1 and 4 min. As a reference sample, we chose an emulsion formulation containing 17.5% w/v polymer in the organic solution, 1.43% w/w paclitaxel (relative to the polymer load), and an organic to aqueous (O:A) phase ratio of 2:1 v/v. All other formulations are presented in Table I. Surface active agents were added to the emulsion in some of the samples: pluronic (1% w/w relative to the polymer quantity) was added to the polymer solution and PVA (1% w/v relative to the water quantity) was added to the water.

Core/shell fiber structure formation

The treated core nylon fibers were dip-coated (while placed on holders) in fresh emulsions and then frozen immediately in a liquid nitrogen bath. The holders + samples were then placed in a precooled (−105°C) freeze drier (Virtis 101 equipped with a nitrogen trap) capable of working with organic solvents (freezing temperature of the condenser was ~−105°C), and freeze dried in order to preserve the microstructure of the emulsion-based core/shell fiber structures. That is, this process of freeze drying enables sublimation of water from the aqueous phase and solvent from the organic phase, leaving solid polymeric structure with pores inside.

Drying was performed in two stages:

1. The freeze drier chamber pressure was reduced to 100 mTorr, while the temperature remained at −105°C.

Morphological characterization

The morphology of the composite core/shell fiber structures (cryogenically fractured surfaces) was observed using a Jeol JSM-6300 scanning electron microscope (SEM) at an accelerating voltage of 5 kV. The SEM samples were Au-sputtered prior to observation. The structure of the shell (coating) surface was also observed for certain samples. The mean pore diameter of the observed morphologies was analyzed using Sigma Scan Pro software, and statistics were drawn using SPSS. Statistical significance was determined using the ANOVA (Tukey-Kramer) method. The effects of the emulsion’s composition and processing parameters on the microstructure were studied by examining the following parameters:

1. Paclitaxel content (% w/w, measured relative to the polymer weight).

### Table I

<table>
<thead>
<tr>
<th>Amount</th>
<th>Mean Pore Size (μm)</th>
<th>Porositya (%)</th>
<th>Coating Thickness (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymer content (% w/v)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>5.8 ± 2.3</td>
<td>58</td>
<td>27.7 ± 3.6</td>
</tr>
<tr>
<td>17.5</td>
<td>6.5 ± 2.3</td>
<td>85</td>
<td>104 ± 3.4</td>
</tr>
<tr>
<td>22.5</td>
<td>5.4 ± 2.1</td>
<td>82</td>
<td>64.2 ± 32.4</td>
</tr>
<tr>
<td>Paclitaxel content (% w/w)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6.9 ± 1.9</td>
<td>N/A</td>
<td>42.2 ± 3</td>
</tr>
<tr>
<td>0.71</td>
<td>5.4 ± 2.6</td>
<td>89</td>
<td>74.2 ± 9.9</td>
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<tr>
<td>1.43</td>
<td>6.5 ± 2.3</td>
<td>85.2</td>
<td>104 ± 31.4</td>
</tr>
<tr>
<td>2.86</td>
<td>21.2 ± 6</td>
<td>85</td>
<td>81 ± 37.7</td>
</tr>
<tr>
<td>7.14</td>
<td>79.1 ± 17</td>
<td>N/A</td>
<td>192.8 ± 90.7</td>
</tr>
<tr>
<td>Organic to aqueous phase ratio (v/v)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4:1</td>
<td>6.1 ± 3.1</td>
<td>87.6</td>
<td>52.3 ± 12.5</td>
</tr>
<tr>
<td>2:1</td>
<td>6.5 ± 2.3</td>
<td>85.2</td>
<td>104 ± 31.4</td>
</tr>
<tr>
<td>1.3:1</td>
<td>7.8 ± 3.8</td>
<td>94.2</td>
<td>64.6 ± 24.1</td>
</tr>
<tr>
<td>Surfactant content (% w/v)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>6.5 ± 2.3</td>
<td>85.2</td>
<td>104 ± 31.4</td>
</tr>
<tr>
<td>Pluronic</td>
<td>8.2 ± 3.0</td>
<td>88</td>
<td>204.1 ± 129.3</td>
</tr>
<tr>
<td>PVA</td>
<td>6.2 ± 2.8</td>
<td>87.5</td>
<td>77.5 ± 24.7</td>
</tr>
<tr>
<td>Homogenization duration (s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>7 ± 3.7</td>
<td>86.8</td>
<td>23.8 ± 1.3</td>
</tr>
<tr>
<td>180</td>
<td>6.5 ± 2.3</td>
<td>85.2</td>
<td>104 ± 31.4</td>
</tr>
<tr>
<td>240</td>
<td>5.9 ± 2.6</td>
<td>81.6</td>
<td>90.2 ± 44.7</td>
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<td>Homogenization rate (rpm)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>5500</td>
<td>7.7 ± 3.5</td>
<td>92.7</td>
<td>114.6 ± 33.2</td>
</tr>
<tr>
<td>16,500</td>
<td>6.5 ± 2.3</td>
<td>85.2</td>
<td>104 ± 31.4</td>
</tr>
<tr>
<td>25,000</td>
<td>5.8 ± 1.9</td>
<td>86</td>
<td>65.7 ± 20.7</td>
</tr>
</tbody>
</table>

aThe measurement error of the porosity is 10%.

1. The condenser was turned off and its plate temperature slowly increased to room temperature, while the pressure was monitored between 100 and 700 mTorr. During this step, the liquid nitrogen trap condensed the excess water and solvent vapors.

The samples were stored in desiccators until use.
2. Polymer content (% w/v, measured relative to the solvent volume).
3. Aqueous to organic phase ratio (v/v).
4. PDLGA copolymeric ratio.
5. Addition of surface active agents.
6. Duration and rate of homogenization.

Microstructure characterization included the following parameters:
1. Mean pore diameter and distribution.
2. Porosity and pore structure.
3. Interconnection between the pores.
4. Coating thickness and adhesion quality.

**In vitro paclitaxel release studies**

Four samples of a chosen composite core/shell fiber were immersed in PBS at 37°C for 112 days. The medium was (completely) removed periodically and fresh medium was introduced. The paclitaxel content of each medium sample was determined using Agilent 1100 high performance liquid chromatography, as described in detail elsewhere.10

**RESULTS AND DISCUSSION**

A SEM fractograph showing the bulk morphology of the reference specimen is presented in Figure 1(b). The quality of the interface between the fiber and the porous coating is high, that is, the surface treatment enabled good adhesion between core and shell. The shell’s porous structure contains round-shaped pores of 6.5 ± 2.3 μm, with a porosity that exceeds 85% (Table I). It can be noted that the shell’s microstructure is uniform, probably due to the rapid quenching of the emulsion which enabled the preservation of its microstructure. The surface of the coating is homogeneously and continuously porous [Fig. 1(c)]. A pore hierarchy is observed, in which the primary structure demonstrates 20–30 μm regions composed of 5-μm pores [Fig. 1(d)]. This may be explained by the fact that the surface is more reactive than the bulk, thus producing a strong tendency to coalesce. The small pores may indicate that a finer surface structure could have been formed if the surface was more stable. Cumulative release of paclitaxel from a selected specimen for 4 months is presented in Figure 2. It can be seen that paclitaxel is released in an exponential manner, that is, the rate decreases with time. Such a release profile is typical of diffusion-controlled systems. A minor burst effect of less than 3% was obtained during the first day of release.

The shell’s microstructure may affect the drug release profile and can also serve as a good measure of the emulsion’s stability. The microstructure is determined by both thermodynamic and kinetic parameters. Thermodynamic stabilization is governed by the emulsion’s formulation, that is by the polymer and drug contents, the O:A ratio, surfactants and copolymer composition, whereas the kinetic considerations are actually the processing conditions, which include the duration and rate of homogenization. The effects of these thermodynamic and kinetic parameters on the shell’s microstructure and the emulsion’s stability are described later in detail.

**Polymer content**

A relatively narrow polymer content range of 15–22.5% w/v was used in this study. Polymer contents below 15% w/v produce a nonhomogenous structure reflected by a partially porous structure, because of the emulsion’s instability, whereas early phase separation of the emulsion occurs at polymer contents above 22.5% w/v, since the organic phase is rapidly rejected by the water. An optimal polymer content range of 15–22.5% w/v was therefore used, in which a relatively stable and homogenous porous structure was achieved. The effects of polymer content on the morphological characteristics of the shell in this range are presented in Figure 3 and Table I. The polymer exhibited only a minor effect on the shell’s porosity and mean pore size. In contradistinction, the coating thickness was extremely thin (27.7 μm) when the polymer content was 15% w/v and increased to 100 μm when the polymer content was increased to 17.5% w/v. The interface quality also improved with the increase in polymer content, probably due to friction forces that were enhanced by the increased viscosity.

According to the theory of emulsion stability, polymer content affects an emulsion’s stability either by increasing its viscosity or by promoting surface stability.13 The viscosity of the organic phase is exponentially dependent on the density of the organic polymer solution. Higher viscosity reduces the tendency of droplets to move up, which leads to breaking of the emulsion. In addition, higher viscosity reduces the dif-
The effects of drug content on the shell’s morphological characteristics are presented in Figure 4 and Table I. The mean pore diameter increased significantly from ~6 μm for samples with a drug content of 0–1.43%, to 79 μm for samples with 7.14% paclitaxel. Since paclitaxel is a hydrophobic drug, its presence in the emulsion’s organic phase changes the emulsion’s hydrophobic–hydrophilic balance. Furthermore, specific interactions such as hydrogen bonds can form between the drug and the host polymer. Higher paclitaxel contents thus decrease the surface tension of the organic phase, that is, increase the interfacial tension between the water and the organic phase, thus resulting in lower emulsion stability. The dispersed droplets tend to either aggregate irreversibly or accumulate at an interface in order to reduce the interfacial energy. Larger pores are therefore created with a higher paclitaxel content.

The emulsion achieved using a high drug content was more viscous and exhibited better adhesion to the core fiber. Consequently, the coating thickness greatly increased with drug load. However, the pores lost their round shape at drug contents that exceeded 1.43% w/w and were distorted or collapsed.

**Organic:Aqueous (O:A) phase ratio**

The effects of the O:A phase ratio on the coating’s structural characteristics are presented in Figure 5 and Table I. At the microstructure level, the size of the pores, the pore distribution, and the porosity presented a trend of an increase with the increase in the aqueous phase content. The increase in pore size between 4:1 samples and 2:1 samples is insignificant, while a significant increase in pore size and distribution is achieved between 4:1 and 1.3:1 samples. It should be mentioned that relatively narrow range of O:A values (2:1 and 4:1) are allowed in this system, in order to achieve stable emulsions.

Theoretically, the overall pore volume as reflected by the size and area of the pores is expected to decrease with the increase in the O:A ratio. Thus, lower porosity is obtained when using a low water content,
and as a result the wall thickness (between pores) increases. The large difference in the surface tensions of the two phases (enhanced by paclitaxel molecules in our formulation) did not allow the creation of high O:A ratios emulsions, and therefore this parameter did not have a significant effect on the microstructure. Whang et al.\(^1\)\(^7\),\(^1\)\(^8\) also investigated inverted PDLGA emulsions, and their results correlated with theoretical expectations when using proteins as a release agent. Furthermore, one of our previous studies\(^9\) showed that using higher O:A ratios, such as 8:1 v/v and 16:1 v/v, significantly decreased the mean pore diameter. In that research the released agent was a relatively high molecular weight protein that acted as a surfactant with a stabilizing effect, and high O:A ratios were beneficial for the release profile of the water-soluble protein. However, in the present study, high O:A values are not required, since low porosity will reduce the release rate of the hydrophobic paclitaxel. If high O:A ratios were required, surfactants could be added in order to stabilize the emulsion.

A specimen of 1.3:1 v/v was fabricated and characterized in order to measure the maximal possible quantity of the aqueous phase, and consequently define the maximum porosity. SEM observations indicated a maximal porosity of 94\% and a nonhomogenous coating with a very large pore size distribution, reflecting low emulsion stability. Hence, in this specific system, O:A ratios lower than 2:1 cannot create a stable inverted emulsion.

Figure 4. SEM fractographs of composite fibers showing the effect of paclitaxel content on the shell’s microstructure. Paclitaxel contents used: (a) 0.71\% w/w, (b) 1.43\% w/w, (c) 2.86\% w/w, (d) 7.14\% w/w. (e) Pore diameter distribution: □ 0.71\% w/w paclitaxel, ■ 1.43\% w/w paclitaxel, □ 2.86\% w/w paclitaxel, 7.14 \% w/w paclitaxel.
Incorporation of surfactants

Surfactants were incorporated in order to study their effect on the emulsion’s stability. It was assumed that a decrease in mean pore diameter would be obtained with the addition of surfactants. Therefore, Pluronic L121 and PVA were chosen based on previous studies that included surfactants in paclitaxel-containing PDLGA emulsions.

The effects of Pluronic on the shell’s structure are presented in Figure 6 and Table I. It can be seen that the morphology changed completely and exhibited very dense pore populations with a small mean pore diameter, surrounded by very large voids where the porosity remained constant. The microstructure gives the impression that emulsion aggregates are formed, rather than the familiar continuous emulsion structure. Water was probably rejected from the dense porous regions and formed the secondary structure with large voids between areas of primary structure. Furthermore, the coating is relatively thick, and better adhesion between core and shell is achieved.

The effects of PVA as a surfactant on the shell’s microstructure are presented in Table I. The emulsion stability and mean pore diameter were hardly affected by the addition of 0.5–10% w/v PVA in the aqueous phase. Higher PVA concentrations resulted in a direct emulsion in the form of microspheres rather than an inverted emulsion.

According to Bancroft’s rule, a direct emulsion is typically obtained with a water-soluble surfactant, whereas an inverted emulsion is more easily obtained with an oil-soluble surfactant. PVA is soluble in water, whereas Pluronic L121 is soluble in oil because of its low hydrophilic lipophilic balance (HLB < 7). PVA therefore did not stabilize the “water in oil” emulsion.
inverted emulsion. Another explanation is in the spatial ring structure of the large hydrophilic vinyl alcohol chain in PVA, which favors an o/w system rather than a w/o system.\textsuperscript{20} In contradistinction, Pluronic L121's long hydrophobic poly(propylene oxide) (PPO) segments anchor themselves in the organic phase, whereas the hydrophilic poly(ethylene oxide) segments (10% w/w) extend into the aqueous medium producing a curvature favoring a w/o emulsion, stabilizing the emulsion and reducing the mean pore diameter. Unfortunately, Pluronic's hydrophobic PPO blocks interact with the PDLGA clews to form PDLGA aggregates, resulting in early phase separation between the aqueous and organic phases.\textsuperscript{19,23} Therefore, in our study, the aggregated PDLGA clews resulted in the formation of large aqueous-rich domains, which transform into large voids following freeze drying. Consequently, the achieved pore structure is uniform in certain regions of very small mean pore diameter surrounded by large voids. A less hydrophobic higher molecular weight surfactant should be selected in order to eliminate these voids and further reduce the size of the pores.

**Copolymer composition**

The effect of the copolymer composition, that is, the relative quantities of lactic acid (LA) and glycolic acid (GA) in the copolymer, was studied on films. These thin films were prepared using the same emulsion preparation technique and were then cast into small aluminum molds and freeze-dried. The resulting structures are presented in Figure 7. The mean pore diameter increased with the increase in LA content in the copolymer. For example, copolymer compositions of 50/50, 75/25, and 100/0 exhibit pore diameters of 1–2 μm, 3–7 μm, and 20–40 μm, respectively. An increase in the copolymer’s LA content actually increases the surface tension, prompting the water droplets toward floccula-
tion and coalescence, and therefore increasing the mean pore diameter in the same manner as addition of paclitaxel affects the emulsion.

**Processing conditions**

The effects of the duration and rate of homogenization on the structural characteristics of the porous shell are presented in Table I. The mean pore diameter and its distribution slightly decreased with the increase in homogenizing time from 60 to 240 s. Thus, a longer duration of homogenization produces a more homogeneous pore structure with a smaller mean pore diameter, which occurs because more droplets are fragmented and refragmented. The homogenization rate also slightly affects the mean pore diameter and distribution, both of which decreased at higher stirring rates \( (p < 0.05 \) between all specimens). Higher fragmentation energy increases the shearing rate producing finely dispersed water droplets, whereas energy is continuously lost due to friction between the viscous emulsion and the homogenizer blades. These results are in agreement with those of Bibette et al.\(^{13}\) and Liu and McGrath,\(^{24}\) who investigated “organic in aqueous” emulsions. In can be concluded that in our systems the effect of the emulsion formulation (drug and polymer contents, O:A ratio and surfactants) on the resulting microstructure is more important than the processing conditions.

**Control of the emulsion’s stability**

The emulsion’s stability has a significant effect on the scaffold’s microstructure. Emulsion destruction mechanisms, such as creaming, flocculation, Ostwald ripening, and coalescence, result in an increased pore diameter as well as in poor dispersion of the pores. As reflected in our microstructure characterization, the mean pore diameter can be decreased using three approaches: increasing the viscosity of the emulsion, promoting the surface stability of the water droplets, and increasing the mechanical fragmentation. These methods were applied separately or in combination and resulted in an overall trend of reducing the mean pore diameter of the fiber’s shell while maintaining high porosity levels.

**Emulsion viscosity**

The emulsion’s viscosity is determined by the i.v. of the host polymer, the polymer content of the organic phase, and the O:A phase ratio. The organic phase viscosity is exponentially dependent on the density of the polymer solution, which is determined by the i.v. as well as by the polymer concentration within the organic phase. When viscosity increases over a certain threshold, the velocity of a water droplet is reduced, reducing the creaming rate and consequently promoting stability. High viscosities also reduce the Ostwald ripening rate due to slow diffusion.\(^{13}\) Consequently, high viscosities increase the emulsion’s stability and reduce the obtained microstructure’s pore diameter. Higher viscosity increases the friction forces between the fiber and the coating, and therefore results in better adhesion between core and shell.

**Surface stability**

Controlling the rate of flocculation and coalescence may be achieved by introducing steric forces between the water droplets and the oil (polymeric) medium. Ionic surfactants are not effective within the organic medium due to the low dielectric constant of the organic solvents. Thus, steric stabilization is the key approach in this system.\(^{13}\) Steric stabilization may be achieved using a low HLB surfactant (i.e., Pluronic L121) or by increasing the polymer content or molecular weight.\(^{25}\) An increase in polymer content or surfactant incorporation causes the polymer to bind at the interface between the water and oil phases and stabilizes the emulsion. Surface stability is also obtained with low paclitaxel loads and a lower LA content of the copolymer composition. We have shown that both the drug content and the copolymer composition affect the emulsion’s stability in the same manner. The mean pore diameter increased significantly with the increase in the polymer’s drug content or LA content. This may be explained by the fact that both paclitaxel and LA are hydrophobic. Adding these hydrophobic materials to the emulsion increases the interfacial tension. The dispersed phase (water) tends to reduce the surface tension by aggregation, which is caused by flocculation and coalescence.

**Mechanical fragmentation**

Homogenizing energy (i.e., homogenization rate or duration) causes fragmentation, which reduces the mean pore diameter and distribution. However, the microstructure is less affected by homogenization energy than by the emulsion’s formulation. The homogenization rate may exhibit a greater effect on the microstructure if a more powerful homogenizer is used.

It is not always clear which instability mechanism dominates the system. This fact emphasizes the complexity of our emulsion-based system.

**SUMMARY AND CONCLUSIONS**

New bioresorbable core/shell fiber structures for biomedical and tissue regeneration applications were...
developed and studied. These structures were composed of a nylon core and a porous PDGLA shell loaded with the anti-proliferative agent, paclitaxel, prepared using freeze drying of inverted emulsions. Since the drug was loaded only in the porous shell, these new fibers are designed to combine good mechanical properties with a versatile drug release profile. Investigation of the composite fibers focused on the effects of the emulsion’s composition (formulation) and processing conditions on the porous shell structure, which reflects the emulsion’s stability and also may affect the drug release profile from the fibers.

In general, extremely porous “shell” structures (mean porosity of ~85% and mean pore size of 6 µm) were obtained with good adhesion to the core fiber. The following emulsion parameters were chosen in order to obtain a stable emulsion that will result in a homogeneous porous shell structure and a feasible release profile of the water-insoluble drug: 15–22.5% w/v polymer content in the organic phase, 0.71–2.86% w/w paclitaxel (relative to the polymer), O:A phase ratio in the range of 2:1–4:1, homogenization rates of 2500–25,000 rpm and homogenization durations of 60–240 s.

The emulsion’s drug content and copolymer composition exhibited a significant effect on the shell’s structure. An increase in drug content or in the LA content of the PDGLA copolymer resulted in an increase in pore diameter, mainly due to the more hydrophobic nature of the organic phase. This increased the interfacial surface tension between the two phases and therefore enhanced the emulsion’s instability. A decrease in the O:A ratio resulted in some increase in pore size and porosity. An increase in homogenization rate and duration resulted in a small decrease in porosity and distribution. Thus, in the studied system, the thermodynamic parameters are more important than the kinetic parameters in determining the emulsion’s stability and the shell’s porous structure.

References