Porous morphology and mechanical properties of poly(lactide-co-glycolide) hollow fiber membranes governed by ternary-phase inversion

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1. Introduction

Recently, poly(lactide-co-glycolide acid) (PLGA) hollow fiber membranes (HFMs) have been successfully used for various biomedical applications, where the morphological and mechanical characteristics of HFMs are of crucial importance. This study focused on the effects of fabrication conditions on the morphology and mechanical performance of PLGA HFMs, which were manufactured by a phase inversion-based dry-jet wet spinning process. The cross-sectional morphology of HFMs was found to be significantly influenced by PLGA concentration of dope fluid. A 5-layered microstructure with macrovoids varied to a 6-layered microstructure with sponge-like microvoids when the PLGA concentration increased from 14% to 22%. Also, Young’s modulus and compressive modulus of these PLGA HFMs were found to dramatically increase with PLGA concentration. To understand the underlying mechanism of morphological formation in PLGA HFMs, a physical mass transfer model was developed to describe the mutual distribution of polymer/solvent/nonsolvent in the governing equations, which was validated by the overall agreement between the experimental and numerical results. The present study should be helpful for understanding the formation mechanism of porous morphology during the phase inversion-based dry-jet wet spinning process, which may guide the optimization of PLGA HFMs for their applications as tissue engineered scaffolds.

A B S T R A C T

Due to the controllable biodegradability and good biocompatibility, poly(lactide-co-glycolide acid) (PLGA) hollow fiber membranes (HFMs) have been successfully used for various biomedical applications, where the morphological and mechanical characteristics of HFMs are of crucial importance. This study focused on the effects of fabrication conditions on the morphology and mechanical performance of PLGA HFMs, which were manufactured by a phase inversion-based dry-jet wet spinning process. The cross-sectional morphology of HFMs was found to be significantly influenced by PLGA concentration of dope fluid. A 5-layered microstructure with macrovoids varied to a 6-layered microstructure with sponge-like microvoids when the PLGA concentration increased from 14% to 22%. Also, Young’s modulus and compressive modulus of these PLGA HFMs were found to dramatically increase with PLGA concentration. To understand the underlying mechanism of morphological formation in PLGA HFMs, a physical mass transfer model was developed to describe the mutual diffusion process of PLGA/dimethyl sulfoxide (DMSO)/water ternary system. This model was able to quantify the PLGA distribution within the HFM cross sections by considering the interaction terms of polymer/solvent/nonsolvent in the governing equations, which was validated by the overall agreement between the experimental and numerical results. The present study should be helpful for understanding the formation mechanism of porous morphology during the phase inversion-based dry-jet wet spinning process, which may guide the optimization of PLGA HFMs for their applications as tissue engineered scaffolds.

1. Introduction

Recently, poly(lactide-co-glycolide acid) (PLGA) has been successfully used for various biomedical applications as sutures, drug delivery, implants, prosthetic devices, and tissue engineering scaffolds [1,2], because of its controllable biodegradability and good biocompatibility [3,4]. Hollow fiber membranes (HFMs) have the advantages of high surface area/volume ratio [5,6] over other types of tissue engineering scaffolds, thus PLGA HFMs have been considered as promising tissue engineering scaffolds and widely utilized in the fields of artificial vessels [7], peripheral nerve regeneration [8,9], bioreactors [10,11] and so on. In previous studies, most of PLGA HFMs were prepared by a dry-jet wet spinning process using tube-in-orifice spinnersets [10,11], which is a typical immersion precipitation-based phase inversion process [12] leading to a porous morphology of PLGA HFMs.

The porous morphology of HFMs is considered as one of the crucial factors which influence the successful applications of HFMs as tissue engineering scaffolds. The porous morphology affects cell proliferation, differentiation for tissue regeneration [13] on HFMs, because the porous morphology can facilitate the exchange of nutrients and waste products between the lumen and the outer environment [14,15]. On the other hand, pore size and distribution also affect the susceptibility of the PLGA HFMs towards in vivo swelling and degradation [16]. More importantly, the morphological characteristics of PLGA HFMs, including porosity, pore size and distribution, have been found to significantly influence the mechanical properties of PLGA HFMs [17,18].
Therefore, a systematical understanding of the formation mechanism of porous morphology during fabrication process is of great importance for the practical applications of PLGA HFMs.

During the dry-jet wet spinning process, the porous morphology of polymeric HFMs is formed due to the phase inversion of the polymer/solvent/non-solvent ternary system, where the nonsolvent diffuses into the dope fluid, and the polymer is re-arranged into the polymer-rich and polymer-poor phases because of the mutual diffusion of the components [19]. In this way, the fabrication conditions of the dry-jet wet spinning have been found to effectively influence the morphology of HFMs. First of all, the polymer concentration of dope fluid has been found to play an essential role in regulating the HFM morphology. Therefore, a systematical understanding of the formation mechanism of porous morphology during fabrication process is of great importance for the practical applications of PLGA HFMs.

HFMs. The effects of the flow rate of dope fluid on the HFM morphology are more intriguing. Usually, the increasing flow rate of dope fluid was found to decrease the permeability of membranes [21,23]. However, Ismail and coworkers [24] found that the permeability and pure water flux of membranes were improved when the flow rate of polyethersulfone (PES) dope fluid increased from 3.5 to 4 cm²/min. Moreover, different additives, polyvinylpyrrolidone (PVP) and lithium chloride (LiCl) for example, were added to adjust the pore size of the HFMs [25,26]. The influences of other spinning parameters such as temperature, the air-gap length, the flow rate of bore fluid were also investigated in the previous studies [27–30].

Despite the aforementioned progress in experimental investigations, very few theoretical and numerical studies have been performed to reveal the mechanism of morphology formation in a quantitative manner. Zhou and coworkers [31] developed a phase inversion model to describe the microstructural formation of immersion precipitation-based flat sheet membranes. In this model, a homogeneous liquid-liquid separation was predicted, which was driven by the gradient of chemical potential in the polymer solution. Since only the spinodal decomposition was considered in Zhou’s model, this model is not capable of predicting the formation of layered morphology in HFMs. Fernandes and coworkers [32] developed a model considering the diffusion of the solvent and nonsolvent during the phase inversion process. However, this model neglected the effects of interaction between polymer/solvent/nonsolvent components on the diffusion, which was not accurate enough to predict the polymer distribution in HFMs fabricated by the dry-jet wet spinning. He and coworkers [33] investigated the morphology evolution of flat sheet membranes during the immersion precipitation process with Monte Carlo methods, which have difficulty in describing the dynamics of phase inversion [34].

The purpose of this work is to quantitatively understand the relationship between spinning conditions and morphology formation of PLGA HFMs, which also directly determines the mechanical properties of PLGA HFMs. Here, the influences of dope fluid concentration and flow rate during the dry-jet wet spinning process on the HFM morphology and mechanical properties were experimentally investigated. A mass transfer model was developed to describe the underlying diffusion of the polymer/solvent/non-solvent ternary system, which was able to quantitatively predict the porosity and morphology based on PLGA distribution within HFM cross sections. This work may be useful in guiding the design and optimization of morphology and mechanical properties of polymeric HFMs using the dry-jet wet spinning process.

2. Materials and methods

2.1. Materials

Poly(α-lactide-co-glycolide) (PLGA) 50:50 copolymer (Mw = 60 kDa, and intrinsic viscosity = 0.57 dL/g; Shandong Institute of Medical Instruments, Jinan, Shandong, China) was used as the polymer. Dimethyl sulfoxide (DMSO, purity ≥ 99.0%) was purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China) and used as the solvent without further purification. Deionized water was used as the bore fluid (nonsolvent) and the external coagulant in the spinning process.

2.2. Preparation of HFMs

After being dried at room temperature overnight, the PLGA powder was dissolved in the DMSO to prepare the dope fluid, which was stirred at room temperature for 24 h. Then, the dope fluid was kept standing for 4 h to remove the possible air bubbles before spinning.

The schematic of the dry-jet wet spinning setup is shown in Fig. 1, where the dope fluid and bore fluid were pumped (Harvard Apparatus, United States) with syringes (Hamilton, Switzerland). The spinneret had an inner diameter of 1.4 mm and an outer diameter of 3.2 mm, and its thickness was 0.15 mm. The nascent hollow fibers were extruded into the coagulation bath without further drawing stretch (free fall). This spinning process was carried out at room temperature. The detailed information of this spinning process has been listed in Table 1. The fabricated HFMs were kept in the deionized water for 24 h to remove the residual DMSO [7,35]. The obtained HFM samples were then cut into segments of 8 cm and kept in deionized water for further measurements or analyses.

2.3. Determination of the cloud point curve of ternary phase

The cloud point curve of the PLGA/DMSO/water ternary system was measured or analyses.

### Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Nozzle geometry (mm)</td>
<td>Inner diameter = 1.40</td>
</tr>
<tr>
<td></td>
<td>Outer diameter = 3.20</td>
</tr>
<tr>
<td></td>
<td>Inner tube thickness = 0.15</td>
</tr>
<tr>
<td>Dope fluid flow rate (Qd) (mL/min)</td>
<td>1.6, 2.0, 2.4, 2.8</td>
</tr>
<tr>
<td>Dope fluid concentration (φd) (w/w)</td>
<td>14%, 18%, 22%</td>
</tr>
<tr>
<td>Bore fluid flow rate (Qb) (mL/min)</td>
<td>4.8</td>
</tr>
<tr>
<td>Air gap (cm)</td>
<td>2</td>
</tr>
<tr>
<td>Room temperature (°C)</td>
<td>22</td>
</tr>
</tbody>
</table>

Fig. 1. The setup of the dry-jet wet spinning process for HFMs.
was determined by the titration method as described in the previous study [36]. The PLGA dope solutions with concentrations from 6 to 26% (w/w) were prepared and kept in the sealed glass bottles. The temperature was kept at 22 °C for the PLGA dope solutions using a thermostatic water bath during the titration process, and 5 mL deionized water was slowly added into each PLGA dope solution using a micro-pipette with stirring. Once the turbidity appeared, the addition of deionized water was stopped and the solution was kept stirring for 30 min. When the solution became homogeneous again, more deionized water was added into the solution; otherwise, the cloud point was calculated by the amount of PLGA/DMSO/water in the solution. The cloud point curve of other PLGA concentrations was determined by the linearized cloud point curve correlation [37].

2.4. Characterization of HFM morphology and porosity

The HFM morphology was analyzed by a micro-CT (GE phoenix nanotom® m, Germany) and a scanning electron microscope (SEM, Hitachi SU-8010, Hitachi, Japan). The three-dimensional (3D) map of HFM morphology was obtained with micro-CT, and the porosity of HFM was analyzed by the commercial software VGSTUDIO (Volume Graphics, Germany). To characterize the HFM cross sections, the HFM were fractured after being frozen in the liquid nitrogen for a clean brittle fracture. The SEM images of HFM cross sections were then turned to binarized images to distinguish the pores and dense microstructures, as exemplified in Fig. 2 [38]. The PLGA volume fraction of each cross section (f_v) is calculated according to

\[ f_v = \frac{S_{\text{dense}}}{S_{\text{total}}} \]  

where \( S_{\text{dense}} \) and \( S_{\text{total}} \) are the areas of dense microstructure and the total cross section in the binarized image, respectively. The overall porosity of PLGA HFMs is obtained by

\[ f_p = \left( 1 - \frac{\rho_{\text{HFM}}}{\rho_{\text{PLGA}}} \right) \times 100\% \]  

where \( \rho_{\text{PLGA}} = 1.25 \text{ g/cm}^3 \) is the density of pure PLGA, and \( \rho_{\text{HFM}} \) is the density of PLGA HFMs calculated from

\[ \rho_{\text{HFM}} = \frac{4m}{\pi(OD^2 - ID^2)} \]  

where \( l \) and \( m \) are the length and mass of HFMs, respectively, and \( ID \) and \( OD \) are the inner and outer diameters of HFMs.

2.5. Characterization of PLGA HFMs mechanical properties

The mechanical properties of HFMs were measured by a commercial testing machine (ElectroForce Testbench, TA Instruments). All measurements were carried out at room temperature, and at least 5 specimens were tested for each condition. Young’s modulus of HFMs was measured by the uniaxial stretch at a constant rate of 1 mm/min, and the initial distance between the clamps was 15 mm. To measure the compressive modulus, each HFM sample was cut into 10 mm length and compressed in the radial direction at a rate of 1 mm/min. The compressive strain of HFM cross section is determined as \( \varepsilon = (OD - OD')/OD \) [39,40], where \( OD' \) is the outer diameter after compression [18]. The compressive modulus is defined as

\[ A_0 = \lim_{\varepsilon \to 0} \frac{F}{\varepsilon} \]  

where \( F \) is the compressive force per unit length. The value of \( A_0 \) of each specimen was estimated from the initial slope of its \( F-\varepsilon \) curve [39]. The bending strength of HFMs was determined by the standard 3-point bending test. Intact 12 mm HFMs were placed on the holder at two ends that were 10 mm apart. The third point was lowered by a crosshead from above at the middle point of these two ends with the speed of 1.0 mm/min. The bending strength is calculated through [41]:

\[ \sigma_f = \frac{8F_bL - OD}{\pi(OD^4 - ID^4)} \]  

where \( F_b \) is the yield force determined from the \( F-\varepsilon \) curve, and \( L = 10 \text{ mm} \) is the span length.

3. Mass transfer model of polymer/solvent/nonsolvent ternary system

To understand how the mutual diffusion of involved components affects the formation of HFM morphology, a mass transfer model is developed for the HFM cross sections under polar coordinates (Fig. 3). Several key assumptions have been made in order to describe the dry-jet wet spinning process within the HFM cross sections:

a) There are 3 components in 3 regions: solvent and nonsolvent are in region 1 (bore fluid); polymer, solvent and nonsolvent are in region 2 (dope fluid); and solvent and nonsolvent are in region 3 (coagulant bath).

b) The mass transfer of all the components is assumed to be axisymmetric within the HFM cross sections, i.e., \( \partial/\partial \theta = 0 \) for all the diffusion-related quantities in the governing equations.

c) The polymer is assumed to be kept within the dope fluid (region 2) and will not diffuse across the bore/dope \((L_1)\) and dope/coagulant \((L_2)\) interfaces, which are the inner and outer surfaces of the HFMs.

d) The inner and outer surfaces of the HFMs, \( L_1 \) and \( L_2 \), are assumed to move towards the centripetal direction of the HFMs, due to the shrinkage of \( ID \) and \( OD \) [42–44].

e) The total simulation time of the mass transfer model (dope fluid solidification time) can be defined as the diffusion time when the
composition of dope fluid reaches the binodal equilibrium curve in the ternary phase diagram (Fig. S1 in SI). The total simulation time is estimated as 4.7, 5.7, and 8.8 s for 14%- 18%- and 22%-HFMs, respectively.

For local conservation of mass, the rate of change in the concentrations of individual components should be balanced by the corresponding flux divergence. With the constitutive assumption that the flux of concentration is linearly proportional to the local gradient of spatial distribution of concentrations, we obtain the governing equations of axisymmetric mass transfer of polymer/solvent/nonsolvent between different regions as follows (Fig. 3):

$$\frac{\partial C(i,j)}{\partial t} = \frac{\partial}{\partial r}(rD_{(i,j)}\frac{\partial C(i,j)}{\partial r}) - rX_i C(i,j) \frac{\partial C(i,j)}{\partial r}$$  \hspace{1cm} (6a)

$$\frac{\partial C(2,2)}{\partial t} = \frac{1}{r} \frac{\partial}{\partial r}(rD_{(2,2)}\frac{\partial C(2,2)}{\partial r}) - rX_2 C(2,2) \frac{\partial C(2,2)}{\partial r}$$  \hspace{1cm} (6b)

$$\frac{\partial C(2,3)}{\partial t} = \frac{1}{r} \frac{\partial}{\partial r}(rD_{(2,3)}\frac{\partial C(2,3)}{\partial r}) - rX_3 C(2,3) \frac{\partial C(2,3)}{\partial r}$$  \hspace{1cm} (6c)

$$\frac{\partial C(3,3)}{\partial t} = \frac{1}{r} \frac{\partial}{\partial r}(rD_{(3,3)}\frac{\partial C(3,3)}{\partial r}) - rX_3 C(3,3) \frac{\partial C(3,3)}{\partial r}$$  \hspace{1cm} (6d)

where $C(i,j)$ (kmol/m³) refers to the radial distribution of molar concentration of component $i = P, S, N$ (for polymer, solvent, or nonsolvent, respectively) in region $j = 1, 2, 3$; $D_{(i,j)}$ (m²/s) is the diffusion coefficient of component $i$ in region $j$; $X_i$ ($i = 1, 2, 3$) is the parameter that accounts for individual interaction terms; $r$ is the diffusion time and $r$ is the coordinate in the radial direction. It should be noted that the radial distribution of volume fraction of each component $i$ in region $j$ is

$$\varphi_{(i,j)} = \frac{C(i,j) m_i}{\rho_i}$$  \hspace{1cm} (7)

where $m_i$ and $\rho_i$ are the molecular weight and the density of component $i$, respectively. According to the mass conservation, the radial distribution of polymer concentration can be obtained as

$$\varphi_{(P,j)} = 1 - \varphi_{(N,j)} - \varphi_{(S,j)}$$  \hspace{1cm} (8)

A time-dependent boundary condition is applied on the outer surface of region 2 ($r = R_2$) to consider the effect of air gap. Based on the air gap distance (= 2 cm) and dope fluid flow rate (= 2.4 mL/min) in the experiments, the time of nascent HFMs go through the air gap can be experimentally observed for different dope fluids. Thus, the air gap time used in the simulation is estimated as 0.5, 0.7 and 0.8 s for the 14%- 18%- and 22%-HFMs, respectively. When the nascent HFMs are travelling through the air gap ($0 < t < air gap time$), the boundary condition at $r = R_2$ is

$$\frac{\partial C(i,j)}{\partial r} \bigg|_{r=R_2(t)} = 0, \ i = S, N$$  \hspace{1cm} (9a)

which indicates that the boundary was no mass transfer through the outer surface of L2. When the nascent HFMs come into the coagulant bath ($t \geq air gap time$), the boundary condition at $r = R_2$ becomes

$$C(i,j) \bigg|_{r=R_2(t)} = K_i C(i,3) \bigg|_{r=R_2(t)}, \ i = S, N$$  \hspace{1cm} (9b)

$$\frac{\partial C(2,3)}{\partial r} \bigg|_{r=R_2(t)} = \frac{\partial C(2,2)}{\partial r} \bigg|_{r=R_2(t)}$$  \hspace{1cm} (9c)

The other boundary conditions are specified by:

$$\frac{\partial C(i,j)}{\partial t} \bigg|_{r=0} = 0 \hspace{1cm} i = S, N$$  \hspace{1cm} (9d)

$$C(i,2) \bigg|_{t=t_0} = k_i C(i,1) \bigg|_{t=t_0}, \ i = S, N$$  \hspace{1cm} (9e)

$$D_{(i,1)} \frac{\partial C(i,2)}{\partial r} \bigg|_{r=r_1} = D_{(i,2)} \frac{\partial C(i,2)}{\partial r} \bigg|_{r=r_1}$$  \hspace{1cm} (9f)

$$\frac{\partial C(i,3)}{\partial r} \bigg|_{r=w_2} = 0$$  \hspace{1cm} (9g)

where $L_1(t)$ and $L_2(t)$ are the inner and outer boundaries of region 2 at time $t$, $k_i$ is the partition coefficient of component $i$, $W$ is the boundary of coagulation bath (Fig. 3), which is set as $W \approx R_2$. The axisymmetric boundary condition (Assumption b) is expressed in Eq. (9d), and Eq. (9g) implies that there is no mass transfer through the outer surface of coagulation bath. The conditions of local thermodynamic equilibrium at the dope/bore and dope/coagulant interfaces are described by Eqs. (9b) and (9e); while the continuities of mass transfer at the dope/bore and dope/coagulant interfaces are described by Eqs. (9c) and (9f) [32].

To account for the mass conservation of polymer component in region 2 (Assumption c), the polymer weight in region 2 does not change over time during the phase inversion process, which is

$$\frac{dm_P}{dt} = \frac{d}{dt} \int_{L_2(t)}^{r} \rho r C(2,2) dr = 0$$  \hspace{1cm} (10)

where $m_P$ is the total molecular weight of the polymer. Based on Assumption (d), the time evolutions of the inner and outer surfaces of HFMs are

$$\frac{dL_1(t)}{dt} = v_1$$  \hspace{1cm} and  \hspace{1cm} $$\frac{dL_2(t)}{dt} = v_2$$  \hspace{1cm} (11)

where $v_1$ and $v_2$ are the moving velocity of HFM inner and outer surfaces, respectively (Fig. 3), which can be obtained by the experimental measurements of the displacements of dope/bore and dope/coagulant interfaces before and after HFM solidification. The initial condition in each region is set as: $\varphi_{(N,1)} = \varphi_{(N,3)} = 1$, $\varphi_{(P,2)} = \varphi_{d}$ (Table 1).

The physical parameters of the PLGA/DMSO/water ternary system are listed in Table 2. It is noticed that there are 5 parameters determined by the model fitting: the interaction terms between solvent and nonsolvent gradient ($\chi_1$), solvent and polymer gradient ($\chi_2$) and the...
nonsolvent and solvent gradient ($\chi_3$); partition coefficient of solvent ($k_{(S)}$) and nonsolvent ($k_{(N)}$). These parameters are very difficult to be measured experimentally, but they are important in capturing the mutual diffusion process of the ternary system.

4. Results

4.1. Phase diagram of the ternary system

The ternary phase diagram determined by titration is shown in Fig. 4. Since DMSO has a good miscibility with water, an instantaneous liquid-liquid demixing occurs during the phase inversion process. The binodal curve is close to the polymer/solvent axis, indicating that there is a large region of instability in the phase diagram, thereby resulting in a morphology with large pores in the membranes [48].

4.2. Morphology and porosity of PLGA HFMs

The representative cross sections of PLGA HFMs and their geometry with varying concentrations and flow rates of dope fluid are shown in Fig. 5 and Fig. 6, respectively. The wall thickness of HFMs increases with both dope fluid concentration and flow rate (Fig. 6B), and the concentration of dope fluid is found to have a more pronounced effect on the morphology of HFM cross sections. It can be noticed that the increasing concentration of dope fluid from 14 to 22% results in denser microstructures, thus the overall porosity of HFMs decreases from 88% to 78% (Fig. 6A). In contrast, the variation of overall porosity is less than 1% when the flow rate of dope fluid increases from 1.6 mL/min to 2.8 mL/min, despite different concentrations of dope fluid (Fig. 6A).

Similar to the effects of the concentration and flow rate of dope fluid on the overall porosity of HFMs, the concentration of dope fluid was also found to be responsible for the change in HFM morphology. Similar 5-layered microstructures are observed in the cross sections of 14%- and 18%-HFMs, as shown in Fig. 7A and B. The dense skin layers appear at the locations near both inner and outer surfaces, each connecting to a finger-like layer. A middle layer with sphere-like macrovoids appears between two finger-like layers; while the macrovoids shrink when the concentration of dope fluid increases from 14% to 18%. In contrast, a 6-layered microstructure is observed in the cross section of 22%-HFMs (Fig. 7C). There are two important points from the observation: first, a sponge-like layer with microvoids appears adjacent to the middle layer; second, the sphere-like macrovoids in the middle-layer are suppressed into finger-like macrovoids. Overall, a much denser morphology is formed when the concentration of dope fluid increases during the HFM fabrication.

As shown in Fig. 8, micro-CT provides the 3D map of HFM morphology. Both the cross-sectional micro-CT images on the x-y and y-z planes show the layered microstructures. The SEM images on the x-y and y-z planes are shown in Fig. 7. Based on the 3D map of 14%-HFM morphology (Figs. 7 and 8), the layered microstructure can be observed from different directions of the 3D morphology, but pore shape in the same layer is found to be slightly different on different planes. In the x-y plane, the porous structure extends in the radial direction; while, in the y-z plane the porous structure does not strictly extend in the radial direction.

4.3. Mechanical properties of PLGA HFMs

The influences of the concentration and flow rate of dope fluid on the mechanical properties of HFMs are shown in Fig. 9, in which the concentration of dope fluid plays a more important role. The 14%-HFMs exhibits a low Young's modulus about 20 MPa, which becomes about 130 MPa for 22%-HFMs. In comparison, there is a slight increase of Young's modulus (about 10 MPa) when the flow rate of dope fluid increases from 1.6 to 2.8 mL/min (Fig. 9A). The compressive modulus is also significantly enhanced when the concentration of dope fluid is increased. For example, when the flow rate of dope fluid is 2.0 mL/min, the compressive modulus for 22%-HFMs is about two times of that for 18%-HFMs and three times for 14%-HFMs. Also, the compressive modulus increases with the flow rate of dope fluid (Fig. 9B) under different dope fluid concentrations. For bending strength in Fig. 9C, it can be observed that the 18%-HFMs have the highest bending strength. It is worth mentioning that the 22%-HFMs are more brittle than the 18%-HFMs. From Fig. 9C, all HFMs fabricated with different concentrations of dope fluid show the highest bending strength when the flow rate of dope fluid is 2.4 mL/min.

5. Discussion

The porous morphology and mechanical properties are two key factors for the application of PLGA HFMs as tissue engineered scaffolds, such as nerve conduits. The porous morphology not only significantly affects the mass transportation between the site of injury and surrounding microenvironment, but also effectively influence the mechanical properties of PLGA HFMs. It is therefore imperative to understand the formation mechanism of the porous morphology in PLGA HFMs.

During the dry-jet wet spinning process, the phase separation immediately takes place when the dope and bore fluids contact each other at the spinneret outlet. The interactions between the components of the PLGA/DMSO/water ternary system are shown in the phase diagram (Fig. 4). There is only a very small gap between the polymer/solvent axis and the cloud point curve; thus the composition path of the dope fluid can quickly cross the cloud point curve, and the instantaneous demixing happens once the dope and bore fluids are in contact. Due to the instantaneous demixing, a significant mass exchange between solvent and nonsolvent occurs at the dope fluid/nonsolvent interface, which leads to the phase separation of dope fluid, giving rise to a polymer-rich phase and a polymer-lean one [12]. Therefore, a physical model of mass transfer is of essential importance for the phase inversion
process of the PLGA/DMSO/water ternary system, which can be used to predict the polymer distribution in the dope fluid and provide critical clues on the formation of porous morphology in HFMs.

5.1. Radial distribution of PLGA volume fraction within HFM cross sections

Based on the obtained SEM images of HFM cross sections, the radial distribution of PLGA volume fraction along the HFM wall can be experimentally quantified, and one example is illustrated for a 22%-HFM (Fig. 10A). In parallel, by numerically solving the governing equations of mass transfer (Eqs. (6)–(8)) with the imposed boundary (Eqs. (9)–(11)) and initial conditions, the numerical radial distribution of PLGA/DMSO/water volume fractions along the HFM wall (region 2 in Fig. 3), i.e. \( \phi(P,2) \), \( \phi(S,2) \), \( \phi(N,2) \), can be obtained using the appropriate parameters (Table 2). Fig. 10 shows the comparison of experimental and numerical distributions of PLGA volume fraction in the walls of 14%- (Fig. 10B), 18%- (Fig. 10C), and 22%-HFMs (Fig. 10D), and the mass transfer model is validated by the broad agreement between the experimental and numerical results.

Based on the experimental results in Fig. 10, it is found that the PLGA volume fraction is higher within regions adjacent to the inner and outer surfaces of HFMs prepared with different concentrations of dope fluid, because of the dense skin layers of all HFMs. In the middle zone of 14%-HFMs (Fig. 10B), a low PLGA volume fraction appears due to the macrovoids in the middle layer of 14%-HFMs (Fig. 7A). According to the work by Ren et al. [49], macrovoids form when the nonsolvent diffuses rapidly into the dope solutions, and the nonsolvent extensively replaces the solvent in the dope solution. Since the lower viscosity of dope fluid generally promotes the nonsolvent diffusion, 14%-HFMs form macrovoids with larger pores than those of 18%- and 22%-HFMs (Fig. 7), and no sponge-like microstructures appear in 14%-HFMs. Differently, a peak value of PLGA volume fraction exists within the middle zone of 18%- and 22%-HFMs (Fig. 10C and D), which is caused by the formation of a sponge-like layer with denser microstructure in the middle layer of 18%- and 22%-HFMs (Fig. 7B and C). A higher PLGA concentration suppresses the solvent/nonsolvent exchange due to the higher viscosity of dope fluid. Thus, higher PLGA concentrations of dope fluid lead to the nucleation growth during phase separation [49], which is believed to be responsible for the sponge-like microstructures in 18%- and 22%-HFMs (Fig. 7)[19].

According to the boundary conditions on inner (Eqs. (9b) and (9c)) and outer (Eqs. (9e) and (9f)) surfaces of the mass transfer model (Eq. (6)), there is a significant mass transfer of solvent from dope fluid (region 2) to bore fluid (region 1) and coagulant (region 3), leading to a lower value of solvent volume fraction, \( \phi(S,2) \), on the inner and outer surfaces. This process in the simulation is controlled by the partition coefficients, \( k(S) \) and \( k(N) \), which are defined as the ratio of phase concentration at the inner (\( L_1 \)) and outer (\( L_2 \)) boundaries of region 2. As such, the maximum values of \( \phi(P,2) \) are numerically obtained on the inner and outer surfaces of all HFMs (Fig. 10). Then, the value of \( \phi(P,2) \) decreases from the inner and outer surfaces until two minimum values are reached in the superficial zones close to the two surfaces (Fig. 10C and D). It is caused by the fast diffusion of nonsolvent from bore fluid (region 1) or coagulant (region 3) into dope fluid (region 2), so the value of \( \phi(N,2) \) significantly increases from the surfaces to the middle zone, leading to the decrease of \( \phi(P,2) \) in the superficial zones. In addition, the quick diffusion of the nonsolvent leads to the formation of macrovoids in the HFMs [50], which is confirmed in our experiments (Figs. 7 and 8). Since the PLGA is diffused from the superficial zones to the middle zone, which is driven by the nonsolvent diffusion in the
superficial zones, the value of $\phi_{P,2}$ increases within the middle zone and a local maximum value is achieved in the middle zone for 18%- and 22%-HFMs.

5.2. Influence of the interaction terms in the mass transfer model

It can be noticed from Eq. (6) that the distribution of polymer/solvent/nonsolvent is governed by the Fick's law of diffusion, which includes the interaction terms between polymer/solvent/nonsolvent. The significance of these interaction terms is determined by the values of interaction parameters, $\chi_1$, $\chi_2$ and $\chi_3$, which reduce to the case of Fernandes's model [32] for HFMs without interaction terms when $\chi_1 = \chi_2 = \chi_3 = 0$. The value of the interaction parameters was defined as the solubility or miscibility between the components in the regions. A higher value of the interaction parameters indicates that the miscibility between the components were better in the system, which significantly influence the solution of governing equations (Eq. (6)). Therefore, the consideration of the interaction parameters is the key feature of this mass-transfer model.

The governing role of each interaction term in affecting the radial distribution of cross-sectional PLGA volume fraction, $\phi_{P,2}$, is shown in Fig. 11. The parameter of the interaction between solvent/nonsolvent gradient ($\chi_1$) shows a slight effect on the PLGA distribution when $\chi_1$ increases from 0 to $10^{-12}$ m$^2$/kmol-s, indicating that the interaction between solvent/nonsolvent gradient does not have a strong effect on the diffusion of polymer/solvent/nonsolvent ternary system. The increase of $\chi_2$ (the interaction between solvent/polymer gradient) from 0 to $2.5 \times 10^{-8}$ m$^2$/kmol-s leads to a smoother curve of the radial distribution for PLGA volume fraction, as shown in Fig. 11B. Therefore, a stronger interaction between polymer/solvent leads to a more uniform distribution of PLGA within the HFM cross sections, and the middle sponge-like layer (Fig. 7) would be eliminated. While, the increase of the interaction between nonsolvent/solvent gradient ($\chi_3$) shows an opposite trend to $\chi_2$, leading to a more pronounced peak value in the middle for radial distribution profile of PLGA volume fraction (Fig. 11C). Also, it can be noticed that the elimination of nonsolvent/solvent interaction ($\chi_3 = 0$ in Eq. (6c)) results in a minimum value of PLGA volume fraction in the middle. This suggests that the diffusion equations of polymer/solvent/nonsolvent ternary system (Eq. (6)) cannot predict the existence of sponge-like layer in the middle zone of 22%-HFMs (Fig. 7C) without the interaction between nonsolvent/solvent gradient.

Fig. 7. The x-z plane (1) and the x-y plane (2) of the HFMs with the dope concentration = (A) 14%, (B) 18%, (C) 22%.

Fig. 8. Representative images of micro-CT analysis of 14%-HFM.
5.3. Mechanical properties of PLGA HFMs

The mechanical properties of PLGA HFMs are significantly influenced by their morphological characteristics [18]. As shown in Fig. 9, the mechanical properties (except for bending strength) of HFMs are significantly enhanced with the PLGA concentration in dope fluid, which leads to a denser porous morphology (Fig. 6A). The suppression of macrovoids is considered as the major reason of the improved mechanical properties, leading to membranes failure under high levels of external loading [51]. It should be noticed that the flow rate of dope fluid has a slight effect on the mechanical properties of HFMs compared to the effect of dope fluid concentration (Fig. 9).

In 14%- and 18%-HFMs, the sphere-like macrovoids appear in the middle layer; while the macrovoids are suppressed into finger-like
microstructure in 22%-HFMs, and the sponge-like microstructure fills the gap between the macrovoids (Fig. 7). Thus, 22%-HFMs exhibit a significant increment in Young’s Modulus. By increasing the concentration of dope fluid, the compressive modulus are also greatly enhanced. The bending strength shows a different trend that 18%-HFMs exhibit the highest bending strength, according to the measurements.

6. Conclusion

In this study, the PLGA HFMs were manufactured by the dry-jet wet spinning process. The concentration of dope fluid was found to significantly influence the porous morphology of PLGA HFMs: the cross-sectional morphology of 5-layered microstructure with macrovoids varied to 6-layered microstructure with sponge-like microvoids, when the PLGA concentration of dope fluid increased from 14% to 22%. A ternary phase mass transfer model was established to quantify the mass diffusion/exchange of PLGA/DMSO/water ternary system, which revealed the driving mechanism of morphology formation in PLAG HFMs. In addition, the mechanical properties of PLGA HFMs, including Young’s modulus and compressive modulus, were found to dramatically increase with the concentration of dope fluid. This study should be helpful in understanding the underlying mechanism of morphology formation and how the morphology influences the mechanical properties of PLGA HFMs, which are critical factors for the optimized design/synthesis of PLGA HFMs for their applications in tissue engineered scaffolds.

Acknowledgements

This work was supported by the Key Research and Development Program of Zhejiang Province (2017C01063), the Science Fund for Creative Research Groups of the National Natural Science Foundation of China (Grant No. 51821093), the National Natural Science Foundation of China (No. U16092077 and No. 11702301), the Fundamental Research Funds for Central Universities of China (2017FZA4029), US National Science Foundation (MPM-0600551), and US National Institute of Health (NS050243, NS093985). The authors thank the Yinghua Inspection and Testing (Shanghai) Co., Ltd for performing the micro-CT experiments.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.memsci.2019.02.065.

References


