

Biodegradable Polymer Scaffolds with Well-Defined Interconnected Spherical Pore Network

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ABSTRACT

Scaffolding plays pivotal role in tissue engineering. In this work, a novel processing technique has been developed to create three-dimensional biodegradable polymer scaffolds with well-controlled interconnected spherical pores. Paraffin spheres were fabricated with a dispersion method, and were bonded together through a heat treatment to form a three-dimensional assembly in a mold. Biodegradable polymers such as PLLA and PLGA were dissolved in a solvent and cast onto the paraffin sphere assembly. After dissolving the paraffin, a porous polymer scaffold was formed. The fabrication parameters were studied in relation to the pore shape, interpore connectivity, pore wall morphology, and mechanical properties of the polymer scaffolds. The compressive modulus of the scaffolds decreased with increasing porosity. Longer heat treatment time of the paraffin spheres resulted in larger openings between the pores of the scaffolds. Foams of smaller pore size (100–200 μm) resulted in significantly lower compressive modulus than that of larger pore sizes (250–350 or 420–500 μm). The PLLA foams had a skeletal structure consisting of small platelets, whereas PLGA foams had homogeneous skeletal structure. The new processing technique can tailor the polymer scaffolds for a variety of potential tissue engineering applications because of the well-controlled architecture, interpore connectivity, and mechanical properties.

INTRODUCTION

ENGINEERING TISSUES AND ORGANS with mammalian cells and a scaffolding material is a new approach in contrast to the use of harvested tissues and organs.¹ In the tissue engineering approach, the scaffold plays a pivotal role in cell seeding, proliferation, and new tissue formation in three dimensions.²⁻⁵ Biodegradable polymers have been attractive candidates for scaffolding materials because they degrade as the new tissues are formed, eventually leaving nothing foreign to the body.⁶ A few techniques such as salt leaching,⁷⁻⁹ fibrous fabric processing,^{6,10} gas foaming,¹¹ emulsion freeze-drying,¹² three-dimensional printing,¹³ and phase separation^{5,14-17} have been developed to generate highly porous polymer scaffolds for tissue engineering. These scaffolds have shown great promise in the research of engineering a variety of tissues.¹⁸⁻²⁹ However, to engineer clinically useful tissues and organs is still a challenge. The understanding of the principles of scaffolding is far from satisfactory, and the “ideal” scaffolds are yet to be developed.

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Pore size, porosity, and surface area (surface-to-volume ratio) are widely recognized as important parameters for a scaffold for tissue engineering.^{5,8,30} Other architectural features such as pore shape, pore wall morphology, and interconnectivity between pores of the scaffolding materials are also suggested to be important for cell seeding, migration, growth, mass transport, gene expression, and new tissue formation in three dimensions.^{5,29,31} This paper reports on the development of a novel technique to generate well-controlled interconnected spherical or partially spherical (hollow shell or partial shell) macropores in biodegradable polymer scaffolds.

EXPERIMENTAL PROCEDURES

Materials

Poly(lactide) (PLLA) and poly(lactide-co-glycolide) (85/15) (PLGA85/15) were purchased from Boehringer Ingelheim (Ingelheim, Germany). Poly(vinyl alcohol) (PVA) with a molecular weight of 25,000 and paraffin with a melting point of 53–57°C were purchased from Fisher Scientific (Pittsburgh, PA). Pyridine, hexane, and cyclohexane were purchased from Aldrich (Milwaukee, WI). U.S. standard sieves (100 μm , 250 μm , 350 μm , 420 μm , and 500 μm) were purchased from Newark Wire Cloth Company (Newark, NJ).

Preparation of paraffin spheres

PVA was dissolved in distilled water to make a 0.5% (g/mL) solution. The PVA solution was heated to 60–70°C. Paraffin was heated to melt in a glass vial on a hot plate and was added to the PVA solution. The mixture was vigorously stirred with a magnetic stirring bar with a stirring setting of 6–8 on a hot plate (Fisher Scientific, Pittsburgh, PA). Ice-cold water was poured into the stirred suspension to solidify the paraffin spheres. The suspension containing the paraffin spheres was then poured into a sieve with an opening of 100 μm to sift out the paraffin particles smaller than 100 μm . The paraffin spheres were then washed with distilled water for three to five times to remove the residual PVA. After being dried in air for 1 week, the spheres were sifted with U.S. standard sieve series (100 μm , 250 μm , 350 μm , 420 μm , and 500 μm) to separate them into different size ranges. The paraffin spheres with the desired sizes were collected and stored in a desiccator until use.

Preparation of polymer foam

The paraffin spheres (0.5 ± 0.05 g) were added in a Teflon mold (cylindrical vial with a diameter of 18 mm). The top surface of the paraffin spheres was leveled by tapping the mold on a leveled flat metal plate with three adjustable legs. The mold containing paraffin spheres was then carefully moved into an oven (preheated to 37°C), kept for 20 min unless indicated otherwise, and then cooled down to room temperature. A chosen polymer was dissolved in pyridine to prepare a solution of a desired concentration. Then 0.40 mL of the polymer solution was cast onto the paraffin sphere assembly drop by drop. The mold containing the paraffin sphere assembly and the polymer solution was first maintained under low vacuum (an air pressure of 60 mmHg) to remove the air trapped inside the paraffin sphere assembly. Trapped air appeared as bubbles on the top surface. When no more bubbles were observed, a high vacuum (an air pressure <0.5 mmHg) was used to evaporate the solvent for 2 (PLLA) or 7 days (copolymers). Additional casting and vacuum-drying steps were repeated to produce foams with higher polymer contents (lower porosity).

The dried paraffin/polymer discs were removed from the Teflon mold, and the top layer was cut away with a razor blade to obtain a flat surface. The discs were immersed in 200 mL of hexane to dissolve the paraffin at room temperature for 2 days. The hexane was changed three times a day. The hexane was then exchanged with cyclohexane and the discs were frozen in a freezer (-20°C) for more than 6 h. The frozen foams were freeze-dried in an ice bath for 2 days to remove cyclohexane and they were further dried at room temperature under vacuum for 1 week to remove the solvent completely. The foams were kept in a desiccator until characterization.

Characterization

The density and the porosity of the foams were determined by measuring the dimensions and the mass of the foam.⁵ The skeletal density of the foam, ρ , was calculated as:

$$\rho = \frac{4 m}{\pi d^2 h}$$

where m was the mass, d was the diameter, and h was the thickness of the foam. The porosity, ϵ , was calculated as:

$$\epsilon = 1 - \frac{\rho}{\rho_P}$$

where ρ_P is the density of the polymer. For PLLA foam, ρ_P was determined by:

$$\rho_P = \frac{1}{\frac{(1 - X_c)}{\rho_a} + \frac{X_c}{\rho_c}}$$

where X_c was the crystallinity of the polymer, ρ_a was the density of the amorphous region (1.25 g/mL), and ρ_c was the density of the crystalline region (1.29 g/mL). X_c was given by

$$X_c = \frac{\Delta H_m}{\Delta H_m^o}$$

where ΔH_m was the enthalpy of melting measured with a differential scanning calorimeter (DSC) and ΔH_m^o was the enthalpy of melting for 100% crystalline polymer (203.4 J/g).⁵

Scanning electron microscopy (SEM) (S-3200N, Hitachi, Japan) was used at 5 kV to examine the morphology. In sample preparation, paraffin/polymer specimens were cut into halves with a razor blade before the paraffin was leached out. The paraffin assembly provided the specimens with enough strength to maintain the morphological structure during the cutting. The paraffin was then leached out with hexane and cyclohexane to reveal the porous morphology. The prepared foams were coated with gold using a sputter coater (Desk-II, Denton vacuum Inc.). The gas pressure, the current and the coating time were 50 mtorr, 40 mA, and 200 s, respectively.

The overall three-dimensional arrangement of the pores inside the foam was studied with optical microscopy (Nikon, Model SMZ-2T). The sample was placed on a semitransparent stage and the light source was below the foam so that the pores were the lighter areas on the image due to the higher transmittance of light.

The compressive modulus values of the foams were measured with an Instron 4502 mechanical tester (Instron Co., Canton, Massachusetts). The specimens were porous discs (~ 17 mm in diameter and ~ 3 mm in thickness). The cross-head speed was 0.5 mm/min. The modulus was determined with the initial slope of the stress-strain curve (strain range, 3–8%). When the moduli of different foams were compared, a one-tail Student t -test (assuming unequal variances) was performed to determine the statistical significance (p values < 0.05 were considered significant).

RESULTS

Mechanical stirring and subsequent quenching of the paraffin suspension with ice water produced uniform spherical paraffin particles (Fig. 1A,B). The size of the spheres was controlled in the range of 100–500 μm , with the maximum yield at around 300 μm . The stirring rate and the concentration of the PVA solution were important in controlling the size distribution and the shape of the spheres. Faster stirring rate and higher concentration of the PVA solution resulted in smaller particles with a uniform spherical shape, whereas a slower stirring rate and lower PVA concentration resulted in larger particles, with which a cer-

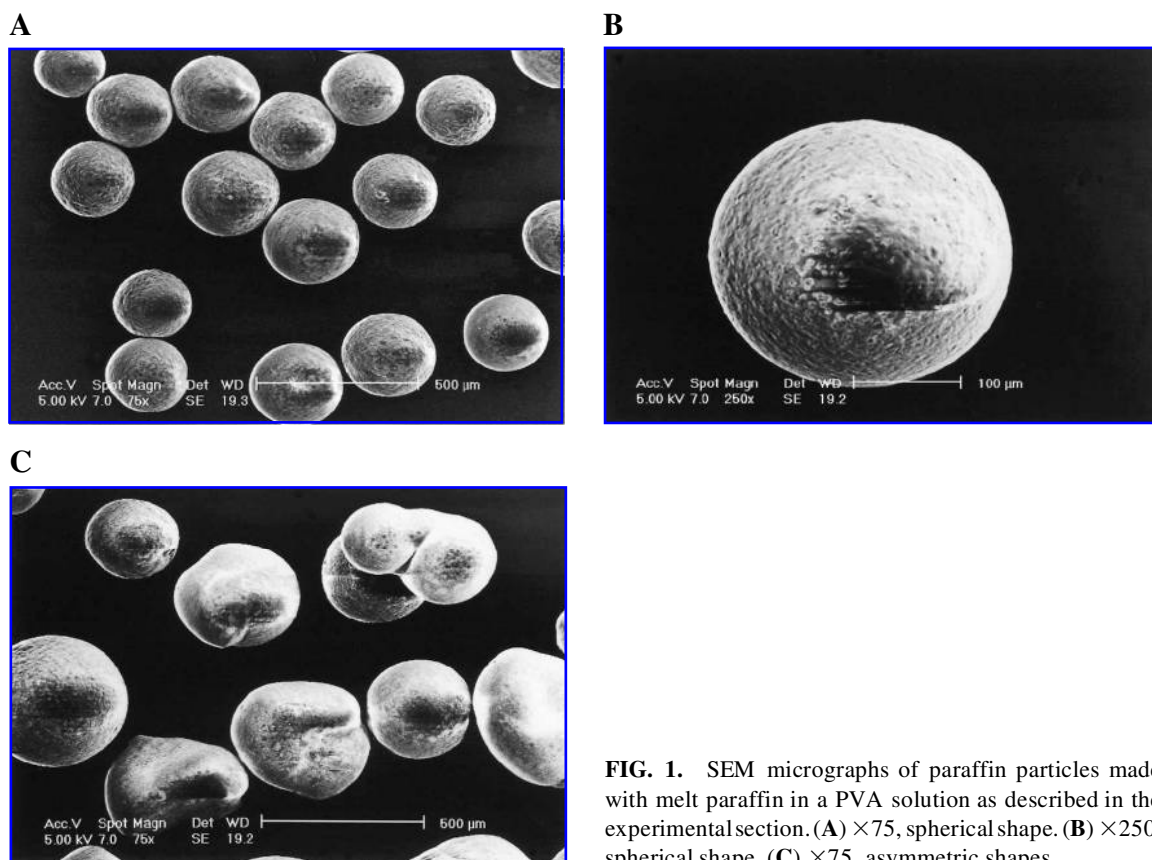


FIG. 1. SEM micrographs of paraffin particles made with melt paraffin in a PVA solution as described in the experimental section. (A) $\times 75$, spherical shape. (B) $\times 250$, spherical shape. (C) $\times 75$, asymmetric shapes.

tain portion of nonspherical particles was found (Fig. 1C). The generation of these undesirable shapes was suppressed by controlling the stirring rate and the concentration of the PVA solution.

The heat treatment at 37°C produced firm bonding between the paraffin spheres to form a three-dimensional assembly (the paraffin spheres began to deform at $33\text{--}34^{\circ}\text{C}$). This treatment ensured the complete connectivity of the pores of the final foam structure after the paraffin was leached out with a solvent/solvents. Because all the spheres were bonded together, no closed pores were generated when the paraffin assembly was removed, as demonstrated in the optical microscopic image of the foam (Fig. 2). The polymer was PLLA, the paraffin spheres were $250\text{--}420\ \mu\text{m}$ in size, and the porosity was about 96%. The polymer skeleton of the foam appeared dark due to the low transmittance of light, whereas the pores appeared light due to the high transmittance of light. The bright areas were the holes connecting the pores. Any closed pore with trapped paraffin would have appeared as a black circle (in the darkest contrast) because of the lowest transmittance of light. However, no black circles were observed, suggesting that all the pores were open and well connected. Another benefit of the heat treatment was the mechanical stability of the resulting paraffin assembly in contrast to the loose paraffin spheres. The loose paraffin spheres could be easily disturbed by a small droplet of polymer solution in the casting step, while the spatial relationship among the bonded paraffin spheres were maintained in the casting process.

PLLA/pyridine solutions of several different concentrations (8%, 10%, 12%, 15%, and 18%) were tested to find an optimal casting concentration at room temperature. It was known that random packing densities of monodisperse spheres were 60–65%.³² The volume fraction of the free space of the packed paraffin spheres, therefore, was approximately 35–40%, neglecting the volume decrease resulted from the bonding between paraffin spheres. The volume of each disc of bonded paraffin spheres was about $0.85\ \text{cm}^3$ and thus a volume fraction of 40% corresponded to 0.34 mL. In our experiments, a 0.40-mL polymer solution was used for each specimen to cover the paraffin disc completely. Different polymer concentrations resulted in

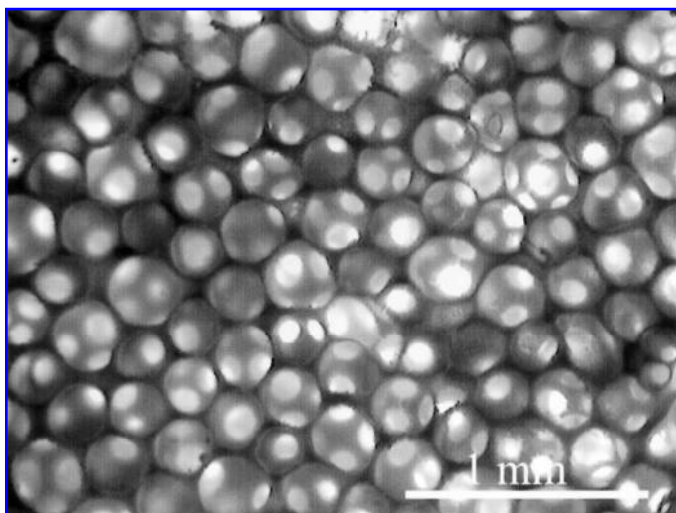


FIG. 2. Optical micrograph of PLLA foam prepared with paraffin spheres with a size range of 250–420 μm and one casting step ($\times 40$).

different porosities (Table 1). In general, a polymer solution of higher concentration produced a denser structure. However, the mechanical properties did not necessarily increase with increasing density of the foams. Properties of the polymer foam made from 8% PLLA solution were too weak to measure. Highly concentrated polymer solutions, such as 15% or 18%, also resulted in relative weak foam formation probably because the high viscosity of the polymer solutions impeded their flow into the interstices between the spheres. As a result, the polymer was not evenly distributed in the disc and weak areas were formed. The concentration of 12% (g/mL) was found to be suitable for casting at room temperature, and this concentration was used for the rest of the study.

Because a porosity of lower than 96% was not achievable with only a single casting of 12% solution, several casting steps had to be repeated to form the denser foams with higher modulus (Fig. 3). For these homogeneous foams, the modulus increased with increasing foam density (decreasing porosity) in a monotonous way. At a porosity of 94.5%, a modulus of about 300 kPa was obtained.

Morphologies of these foams were studied with SEM (Fig. 4). The PLLA foam had a porosity of 95% and the original paraffin spheres were 250–420 μm in size. The pores retained the shapes of the original paraffin spheres and were well connected. The diameters of the cross sections of the individual pores appeared different from each other because the cutting surface intersected the pores at different positions. The openings between the pores were circular in shape and were similar in size. The macropore network was the replica of the surface of the bonded paraffin spheres. In other words, the hollow spherical shell network formed the continuous skeleton of the foam, and the pores were interconnected through the openings formed by the bonding areas of the paraffin spheres. The surface morphology of the pore wall was very similar to that of the new surface exposed by cutting, which indicated that the entire polymer skeleton of the foam

TABLE I. DENSITY, POROSITY, AND COMPRESSIVE MODULUS OF PLLA FOAMS

<i>Polymer concentration</i>	<i>Paraffin sphere</i>	<i>Density (g/cm³)</i>	<i>Porosity (%)</i>	<i>Compressive modulus (kPa)</i>
10% (wt/vol)	250–420 μm	0.032 ± 0.002	96.8 ± 0.2	23.7 ± 18.5
12% (wt/vol)	250–420 μm	0.039 ± 0.003	96.1 ± 0.3	81.8 ± 17.1
15% (wt/vol)	250–420 μm	0.048 ± 0.004	95.2 ± 0.4	46.8 ± 21.3
18% (wt/vol)	250–420 μm	0.042 ± 0.001	95.8 ± 0.1	50.8 ± 13.2

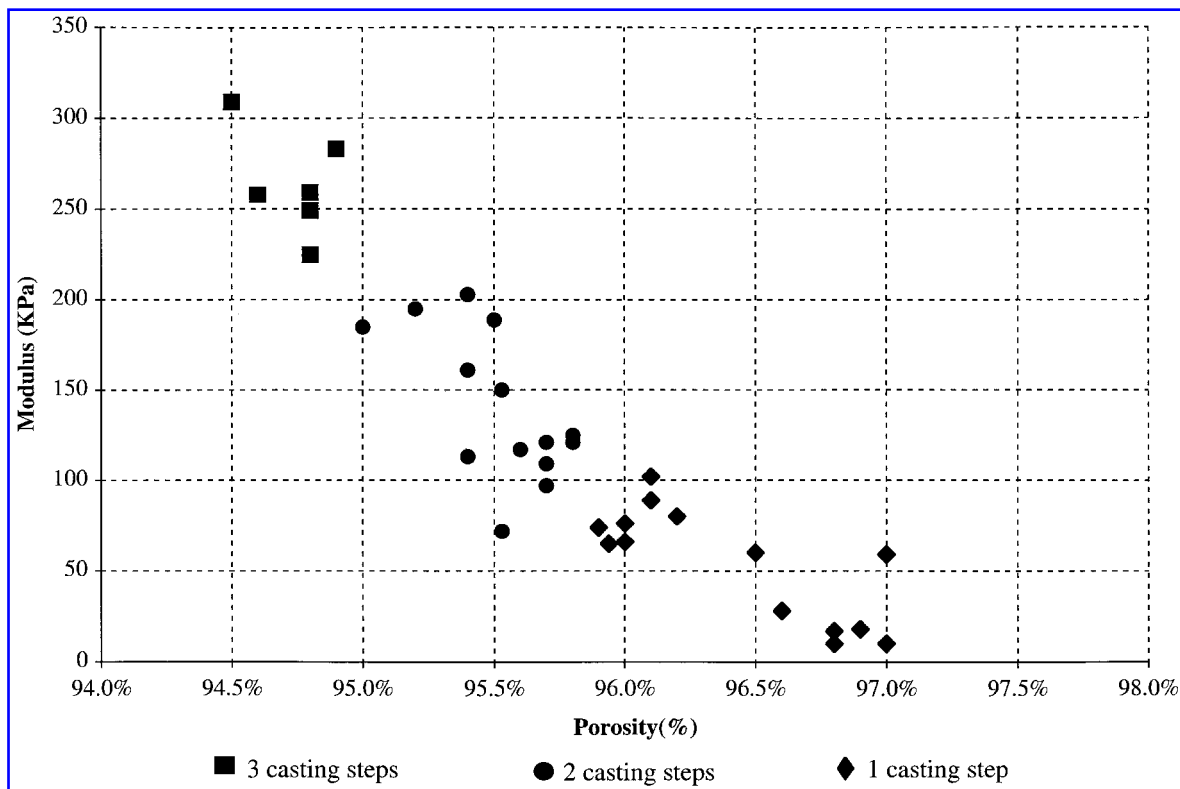


FIG. 3. Modulus versus porosity of PLLA foams prepared with paraffin spheres with a size range of 250–420 μm and different numbers of casting steps.

was uniform in morphology. The polymer skeleton was composed of platelets and irregular micropores between them, similar to the morphology previously observed for PLLA foams prepared without paraffin spheres from different solvent systems at room temperature.⁵ The microporous walls of the macropores could be beneficial to the local mass transport in a scaffold for tissue engineering.

Heat treatment at 37°C for 20 min generated the moderate size of the opening between the pores. It was expected that the size of these openings could be controlled by adjusting the time and the temperature of the heat treatment. To examine the effect of the time of heat treatment on the size of the openings between macropores, paraffin spheres of narrow size distribution (250–350 μm) were treated at 37°C for 20 and 80 min, respectively. The longer time of the heat treatment formed larger bonding areas between the paraffin spheres and resulted in larger openings between the macropores of the polymer foam (Fig. 5).

The mechanical properties of the polymer foams were affected by the pore size (Fig. 6). The PLLA foams prepared with three different sizes of paraffin spheres were controlled at the same porosity level (94.5%). When the paraffin spheres with the size of 100–200 μm were used, the modulus of the formed foam was statistically lower than that of the foams prepared with larger paraffin spheres. The difference between the two larger pore sizes was not statistically significant. The lower modulus of the foams prepared with the smaller paraffin spheres might have resulted from the heterogeneity of polymer distribution because the polymer solution might penetrate with more difficulty into the smaller interstices between smaller spheres, resulting in formation of irregular large pore defects and/or thin pore walls.

Foams were also prepared using PLGA85/15 copolymer (Fig. 7). Paraffin spheres of the sizes of 420–500 μm were used and the concentration of the polymer solution was 12%. Unlike in PLLA foams, neither platelets nor micropores were found either on the surface of the pore wall or in the interior of the polymer skeleton of the foams. The entire structure was homogeneous and well connected. This could stem from the difference in the physical structure of the two polymers. The PLGA85/15 copolymer was amorphous

SPHERICAL PORE SCAFFOLDS

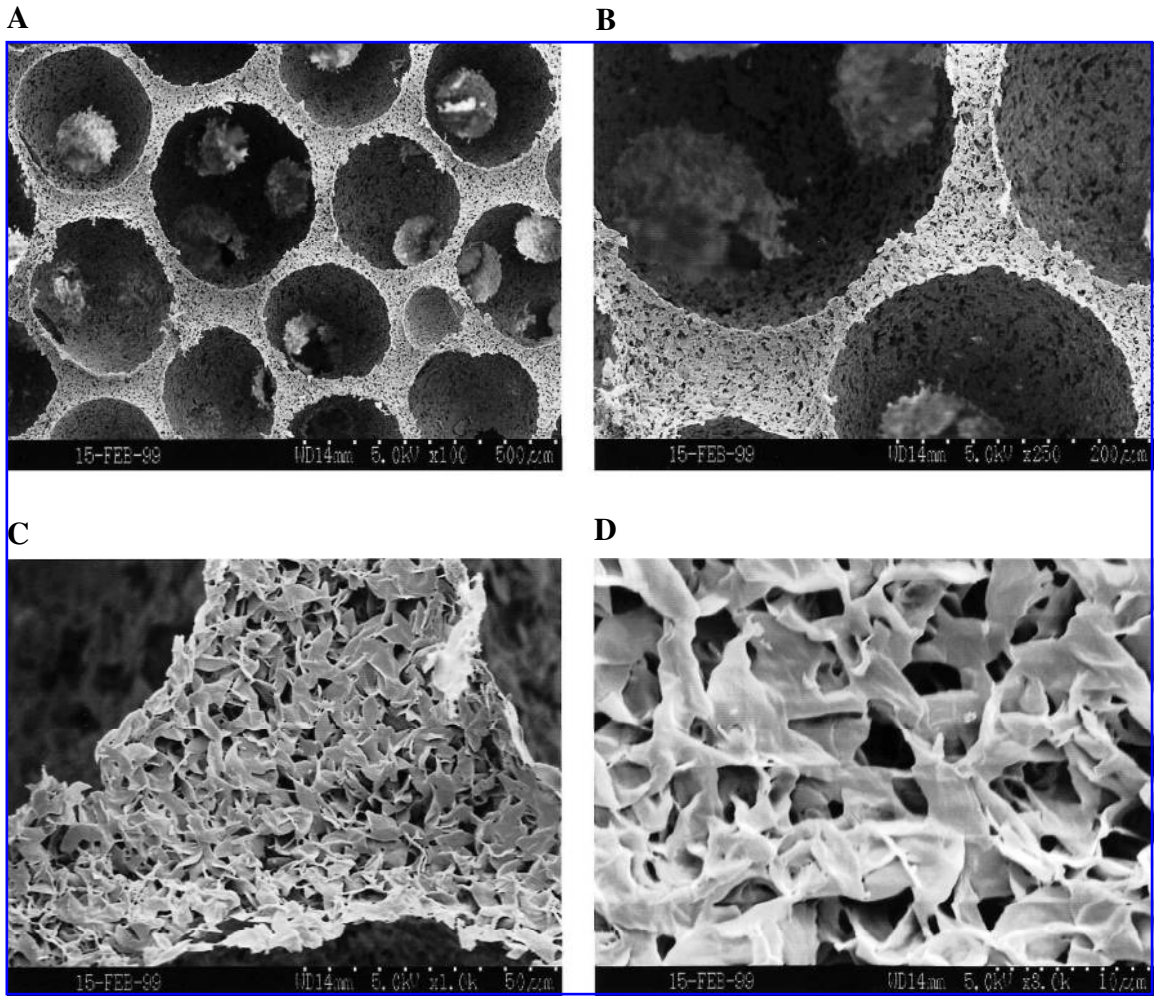


FIG. 4. SEM micrographs of PLLA foams prepared with paraffin spheres with a size range of 250–420 μm and two casting steps. (A) $\times 100$; (B) $\times 250$; (C) $\times 1\text{k}$; (D) $\times 3\text{k}$.

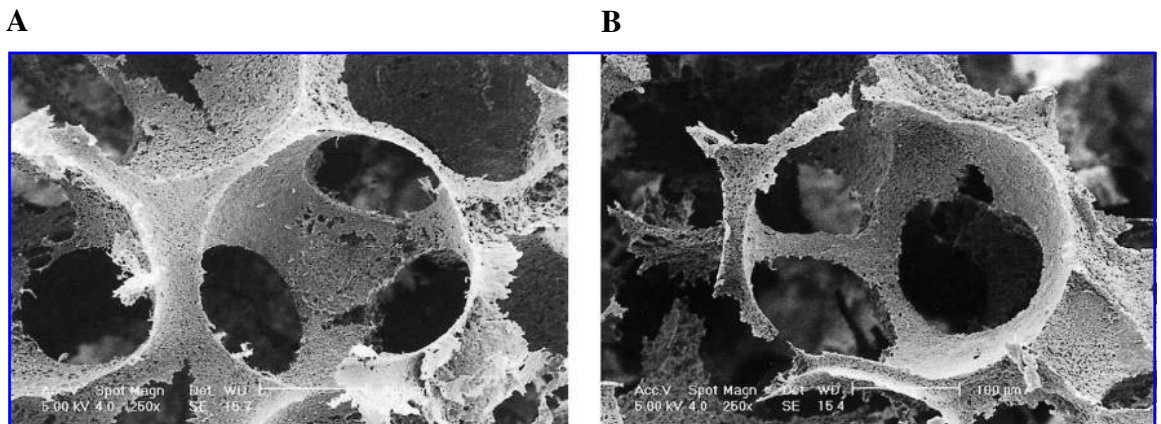


FIG. 5. SEM micrographs of PLLA foams prepared with paraffin spheres with a size range of 250–350 μm and one casting step ($\times 250$). The paraffin spheres were bonded together through a heat treatment at 37°C for different time periods. (A) Heat treatment time, 20 min. (B) Heat treatment time, 80 min.

whereas PLLA was semicrystalline. The platelet structure could be formed through a nucleation and crystal growth process from a crystalline polymer PLLA.⁵ Amorphous polymer PLGA85/15 did not crystallize, therefore only a smoother layer of polymer was deposited on the paraffin spheres. At a high porosity, polymer only covered the connecting areas between the original paraffin spheres (larger connecting lines between spheres or the necklines of the bonding areas), likely due to the surface tension effect of the polymer solution (Fig. 7A,B). The overall interconnected pore architecture was demonstrated in an edge view of the foam (Fig. 7C). At a lower porosity, the open surface of the paraffin spheres was covered more to form a more continuous hollow shell morphology (Fig. 7D).

DISCUSSION

Scaffolding is a critical component in tissue engineering because it provides the three-dimensional clues for cell seeding, migration, growth, and the new tissue formation. Synthetic polymers such as polylactide, polyglycolide, and poly(lactide-co-glycolide) are biodegradable and biocompatible, and are FDA approved for certain clinical applications such as resorbable sutures. Therefore, these polymers are widely exploited as scaffolding materials for tissue engineering. Salt-leaching is a very popular technique to fabricate scaffolds from a variety of polymers, and is well recorded in the literature.^{7,8} In this technique, the polymer (usually in the solution form) is first mixed with NaCl salt crystals to form a polymer/salt composite material (after solvent evaporation). The salt is then leached out with water to form the pores of the polymer foam. The pore size can be controlled by the size of the salt crystals, and the porosity can be controlled by the salt/polymer ratio. However, with the salt-leaching technique, the pore shape is limited to the cubic crystal shape of the NaCl salt, and, more disadvantageously, the interpore connectivity is not controlled. To obtain a spherical pore shape, a technique including compression molding of gelatin spheres and poly-

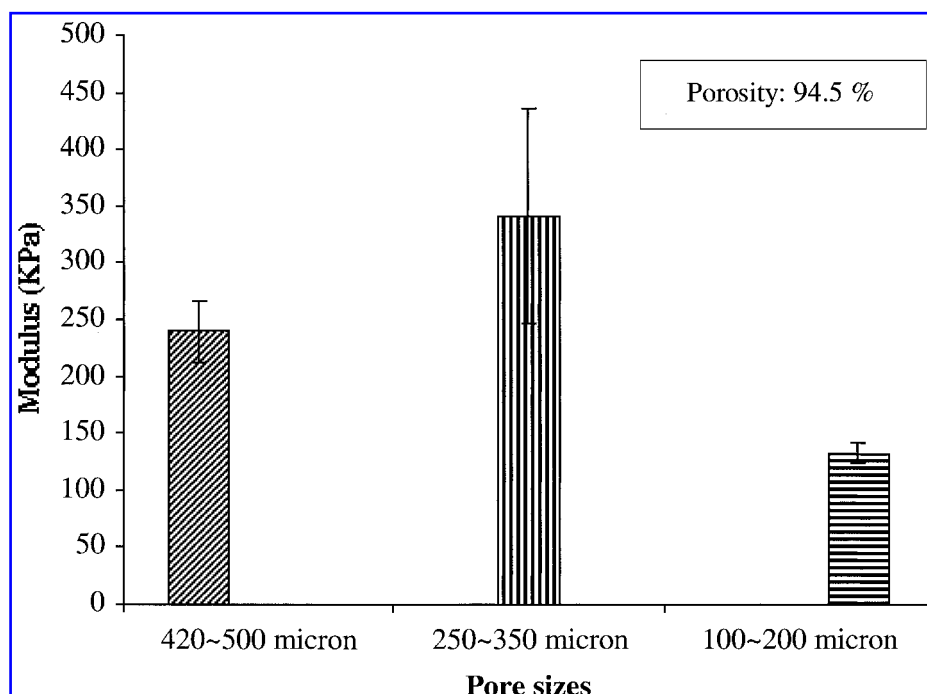


FIG. 6. Pore size effect on the compressive modulus of PLLA foam with three casting steps (porosity, 94.5%). The difference in modulus between the foams of a pore size range of 420–500 μm and 250–350 μm is not statistically significant ($p = 0.357$). The difference in modulus between the foams of a pore size range of 420–500 μm and 100–200 μm , and that between foams of a pore size range of 250–350 μm and 100–200 μm are statistically significant ($p = 0.008$ and 0.032 , respectively).

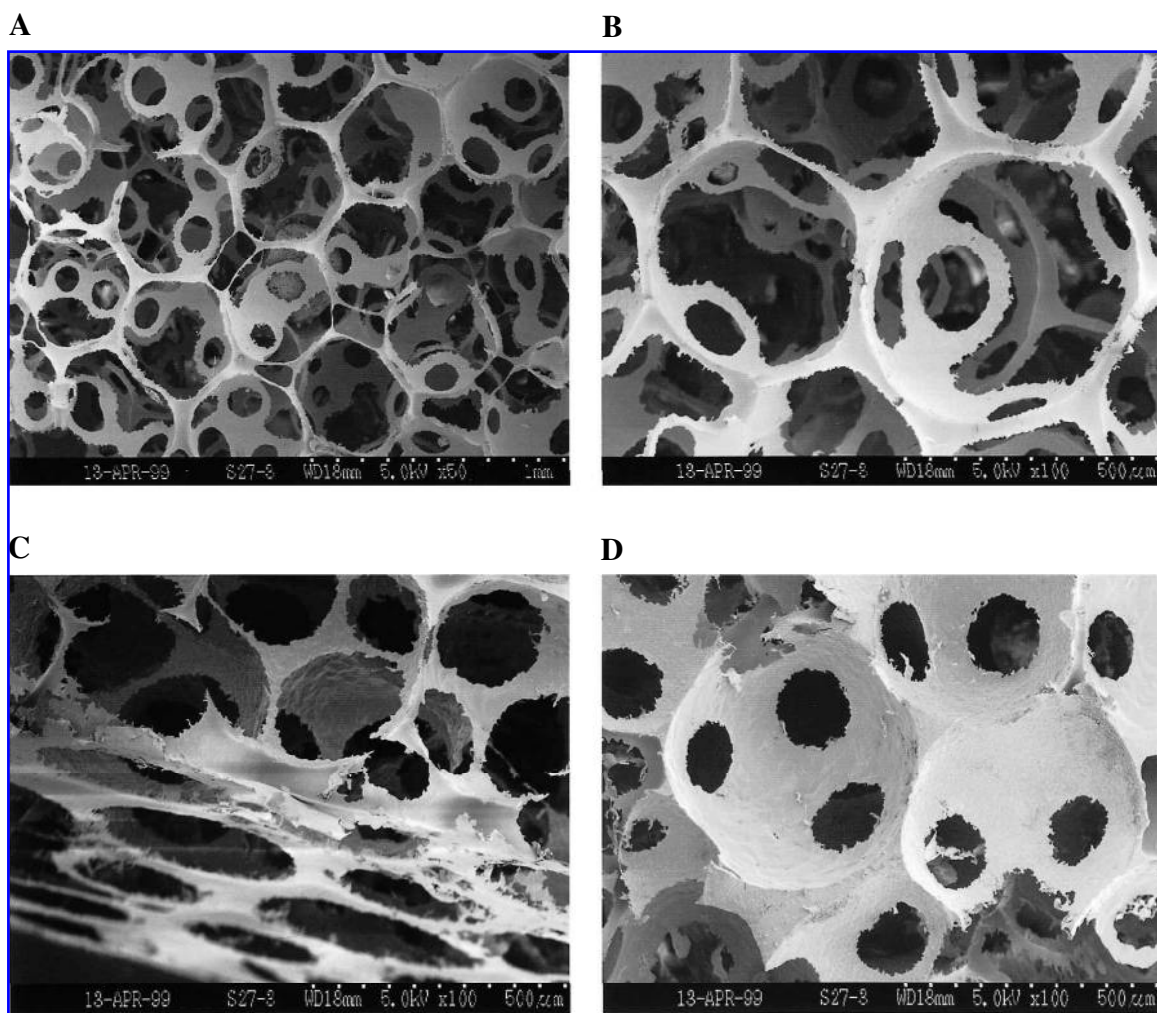


FIG. 7. SEM micrographs of PLGA foams prepared with paraffin spheres with a size range of 420–500 μm . (A) One casting step, $\times 50$. (B) One casting step, $\times 100$. (C) One casting step, $\times 100$, an edge view of the foam. (D) Two casting steps, $\times 100$.

mer powder, and subsequent leaching of the gelatin spheres with water has been reported.⁴ However, that technique is limited to the generation of polymer foams with relatively low porosity (up to around 70%). The interpore connectivity is not well controlled, and residual gelatin in the foams has been reported.⁴

In this work, we have fabricated paraffin spheres as a pore-generating material (porogen) to create spherical pore shape with well-controlled interpore connectivity in the biodegradable polymer foams. The control of the porosity and the pore size was demonstrated by changing the concentration of the polymer solution, the number of casting steps, and the size of the paraffin spheres. Porosity higher than 95% was easily achieved. Furthermore, we have developed a technique to bond these paraffin spheres together to stabilize the structure and, more importantly, to ensure the creation of an interconnected pore network in the polymer foam. We have also demonstrated that the bonding areas between paraffin spheres can be controlled to vary the size of the openings between the spherical pores, which can be very important in controlling cell seeding and distribution in the scaffolds. The processability of the paraffin can also be used to generate other geometrical components to be assembled into more complex structures for architecturally complex scaffolding formation, as we have demonstrated with sugar porogen.³¹ The macroporous architectural design can also be used to improve mass transport and neovasculature formation when implanted *in vivo*.

The macroporous architectural design can be used to vary the flow pattern of the tissue culture medium in these scaffolds in bioreactor cultures and to mediate the fluid mechanical stimulation to engineered tissue constructs. We have further demonstrated that the foam architecture and pore wall structure (platelet like or continuous) are dependent on the polymer (especially the crystallizability) and the polymer concentration used. In addition, the paraffin sphere assembly can be dissolved in some organic solvents (nonsolvents of the polymer) so that certain water-soluble polymers can be involved in the scaffolding materials with this technique, which is important in improving the hydrophilicity of the scaffolding materials when desired.

There are also several advantages in the new fabrication methods. First, there is no sophisticated equipment requirement compared to the textile technology, free-forming, three-dimensional printing, or lithography. Second, the new scaffolding has a homogeneous foam skeleton (either platelet-like or continuous, depending on the crystallizability of the polymer), which is not easily achievable with free-forming, three-dimensional printing or lithography because of their "pixel assembly" nature. Third, the interpore connectivity and the size of the opening between pores are well controlled by the heat treatment process of the paraffin spheres. Fourth, the scaffold can be directly fabricated into a specific anatomical shape with a mold. Fifth, the process can be easily expanded or automated for large-scale production. In conclusion, the new processing technique can tailor the polymer foams for a variety of potential tissue engineering and other biomedical applications because of the well-controlled nature in architecture, interpore connectivity, and physical and mechanical properties.

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