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Fabrication of Biocompatible Blending (PCL/gelatin) Nanofibers using Solution Blow Spinning for Expeditious Control of Hepatic Trauma

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Abstract

Solution blow spinning (SBS) offers an easily adaptable alternative that has the potential to generate on-demand conformal nanofiber mats directly on a wide range of targets. The present study demonstrates the facile fabrication of polycaprolactone (PCL)-gelatin nanofibers using only a commercial airbrush and compressed gas. The PCL content increased mechanical strength, and gelatin content enhanced cell adhesion, proliferation, and acceleration of the biodegradation rate. An animal study was then used to demonstrate some of the possible surgical applications, including use as a surgical hemostatic, as a surgical sealant, and in tissue reconstruction.

Keywords: Solution blow spinning; Gelatin; Polycaprolactone; Hemostatic effect; Massive hemorrhage

Introduction

Acute hemorrhage is the main cause of death in trauma patients [1], with the first minutes after trauma determining the fate of patients; 66.5% trauma deaths occur less than 1 h after injury [2]. The liver is the most commonly injured organ in abdominal cavity trauma [3]. Because of the vascular nature of the liver, injury to this organ can easily lead to catastrophic bleeding and death [4]. In addition, the sinusoidal structure of the liver causes difficulty in maintaining liver tissue hemostasis [5]. Bleeding remains the leading cause of mortality in patients with liver trauma [6]. The high morbidity and mortality rates may not only be attributed to extensive blood loss but also to the long time required to control bleeding [4].

Gelatin has long history as an absorbable, non-toxic biomaterial, and its safety has been proven. This collagen-based degradable product can promote platelet aggregation and is used as a hemostatic agent [8-10]. Studies in the literature have reported that gelatin sponges may have superior hemostatic ability relative to oxidized regenerated cellulose [10, 11]. However, gelatin is a water-soluble and fragile biomaterial therefore, it is often combined with other polymers to enhance its chemical stability and mechanical properties.

Polycaprolactone (PCL) is an aliphatic polyester that has often been used in orthopedic tissue engineering. Previous studies have proven that gelatin and PCL are potential candidates for cartilage tissue engineering for cell attachment, proliferation, and matrix production [12, 13]. Moreover, the addition of PCL to gelatin can increase its mechanical strength and form a porous structure that increases blood absorption [11].

Nanofiber mats and scaffolds have a wide range of biomedical applications, including drug delivery, wound dressing, tissue engineering, and enzyme immobilization [14-17]. Nanofibers are often fabricated by electrospinning, a process that utilizes an electric field applied to a drop of polymer melt or solution on the tip of a nozzle [18, 19]. The droplet deforms, forming a Taylor cone, and a charged jet accelerates toward the target, generating nanofiber [18, 20]. While electrospinning is a powerful and widely studied technique, it requires specialized equipment, high voltages, and electrically conductive targets. It also suffers from a relatively low deposition rate. These restrictions prohibit the use of electrospinning for any in situ deposition of fibers during surgery or for conformal coverage of nonconductive targets without the use of polymer melts [21] or the assistance of air flow [18, 22].

Solution blow spinning (SBS) is a technique that allows the direct deposition of polymer fibers on any substrate. This enables the design of materials that conform to specific anatomical geometries, thus enhancing surgical usability. Solution blow spun polymers offer advantages over preformed nanofiber mats, meshes, and scaffolds that are commonly used in surgical applications [23]. SBS is a promising alternative that requires a simple apparatus, concentrated polymer solution in a volatile solvent, and high-pressure gas source [24].

Numerous polymer systems and deposition conditions have been researched; however, distinct control over the fiber diameter has not been demonstrated [25-29].

Definitive purposes that are advanced are largely analogous to electrospinning and include enzyme immobilization, drug delivery, and microfiltration [30-32]. In electrospinning, polymers are commonly dissolved in highly toxic chlorinated or fluorinated solvents such as dichloromethane, trifluoroethanol, or hexafluoro-e-propanol, which produce narrower, more consistent fibers because of their relatively high dielectric constants [33-35].

Table 1: Associated injuries in 1,086 cases pancreatic trauma [7].

Organ Injury	Patients (%)
Liver	500 (46)
Stomach	449 (41)
Major vascular	300 (28)
Spleen	277 (26)
Kidney	240 (22)
Colon	189 (17)
Duodenum	173 (16)
Small bowel	165 (15)

The SBS technique could be exceedingly useful for the reconstruction of tissue defects such as hernias, the treatment of which requires preformed polymer mats because of a high incidence of recurrent herniation and bowel obstruction [36]. The approach also holds great promise as a surgical sealant in place of or in addition to sutures in applications such as vascular, intestinal, or airway anastomosis [18]. However, these techniques can be technically weak, and when complications of leakage occur, they have high morbidity [37, 38]. Nevertheless, SBS could also be useful in areas requiring the use of a hemostatic material or sealant, especially when large areas are exposed and conventional suturing may not be possible, as in the case with liver and lung resections [39-41].

The key factors in the hemostatic system are blood vessels, platelets, and the coagulation system, which together maintain a closed circulatory system after vascular damage, thus preventing massive loss of blood [42]. In most cases of hemostasis, blood vessels react upon injury, causing arteriolar vasospasms that reduce blood flow at the injury site [43]. The above-mentioned SBS processes can be influenced by nanofibrous hemostatic agents either by supporting thrombin or fibrin production or by supplying binding sites to which platelets or clots can adhere [45].

This work presents the possibility of using nanofibrous sheets as a potential surgical hemostatic agent for massive hemorrhage in hepatic trauma. Polymeric nanofibrous materials were fabricated from PCL and gelatin using SBS. PCL and gelatin are commonly used as biodegradable materials for nanofiber fabrication. These polymers have been investigated as biomaterials for many biomedical applications. Our research focuses on the application of the SBS technique as a surgical hemostatic technique. We prepared a PCL-gelatin mixed solution at various ratios (w/w) and evaluated the hemostatic effects of the nanofiber sheet formed using in vitro and in vivo testing. In particular, in vitro, the PCL-gelatin nanosheets interacted with erythrocytes. Furthermore, we confirmed its biocompatibility, physicochemical properties, and morphology.

Experimental

Materials

Polycaprolactone (average Mn 80,000), Gelatin from porcine skin (Type A) were purchased from Sigma Aldrich. 2,2,2-Trifluoroethanol, 99+% (TFE) was purchased from Alfa Aesar. Acetic acid, glacial, 99.5% (HAc) was obtained from SAMCHUN. A commercial airbrush (Dual Action Airbrush MAX series (MAX-2), 0.25 mm nozzle size (SPARMAX®)) and connected to a compressor equipped with a regulator through a gas flow meter (ZENY, MOEDL: TC-20 series).

Measurements and Characterization

The nanofibers morphology structural properties of the prepared samples were further elucidated by Field-Emission Scanning Electron Microscope (FE-SEM, Hitachi S-4,800). For the physicochemical properties of nanofibers were measured by Thermogravimetric Analysis (TGA, Scinco TGA N-1000), Differential Scanning Calorimeter (DSC, Scinco DSC N-650), Fourier Transform Infrared Spectroscope (FT-IR (ATR mode), Thermo Fischer Scientific Nicolet iS 10), Contact Angle (SEO Phoenix) and Tensile stress-strain (Schimazus Autograph AG-X).

Preparation of Solution Blow Spun Nanofibers

The series of membranes with different PCL-gelatin ratios were fabricated by solution blow spinning. The blow spun solution was made by mixing 6 wt% PCL in trifluoroethanol (TFE) and 6 wt% gelatin in TFE at different mass ratios of 90:10, 60:40, PCL (only), gelatin (only). A tiny amount (0.2 v/v% TFE) of acetic acid was dropped to the solution to get transparent solution. An airbrush was prepared the solution blow spun device in all experiments. The airbrush was connected to a compressor equipped with a regulator through a gas flow meter. The distance from nozzle to target was held constant at 15 cm for all experiments.

Cell culture (AML 12 mouse hepatocyte cell line)

The AML 12 mouse hepatocyte cell line was obtained from American Type Culture Collections (ATCC, Manassas, VA, USA). AML 12 cells were maintained in Dulbecco's Modified Eagle Medium/Ham's F-12 (DMEM/F12; Thermo, Carlsbad, CA USA). The medium was supplemented with 10% fetal bovine serum (FBS; GibcoRBL, Carlsbad, CA, USA), 1% antibiotics (Thermo), 1 x ITS supplement (Insuline-Transferrin-Selenium-G supplement; Invitrogen, Carlsbad, CA, USA) and 40 ng/ml dexamethasone (Sigma Aldrich, St. Louis, MO, USA) at 37 °C in humidified atmosphere with 5% CO_2 in an incubator.

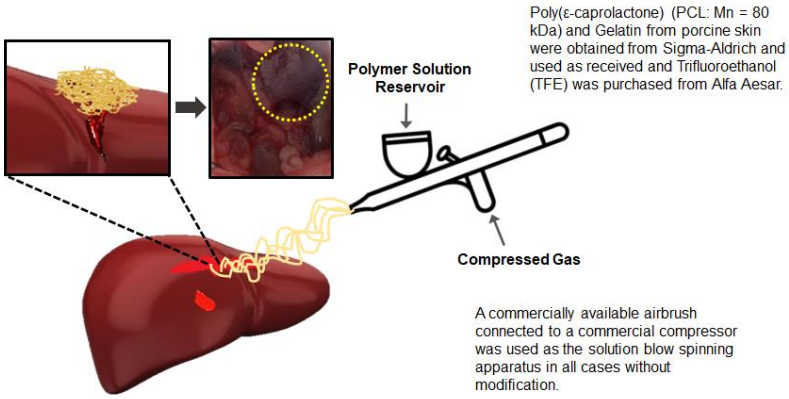
Animal Studies in the Massive Hemorrhage Model

Six-week-old male BALB/c mice (OrientBio, Seongnam, Korea) were used in this study. This study was approved by the "Institutional Animal Care and Use Committee of the Clinical Research Institute" at the Catholic University of Korea (institutional review board: CUMC-2020-0007-10). The mice were anesthetized by intraperitoneal injection of 30 mg/kg tiletamine-zolazepam (Zeletil 20; Virbac, Nice, France). Anesthesia was induced and maintained by mechanical ventilation with isoflurane. A midline laparotomy incision was made extending from the xiphoid to the pubis to expose the intra-abdominal contents. A circumferential intestinal incision was then made, followed by anastomosis with four4 hand-sewn sutures. Two milliliters of 6 wt% PCL in TFE, 6 wt% gelatin in TFE, and PCL-gelatin in TFE (90:10 and 60:40) connected to a compressor was sprayed around the site of anastomosis. After anastomosis, the liver was exposed and superficially injured using a cauterization instrument (~20 mm long and 0.5 mm deep). This was followed by the application of 2 ml of PCL, gelatin, and PCL-gelatin solution under the same deposition conditions. Subsequently, median celiotomy was performed to allow access to the liver. This was followed by segmentectomy of the right liver and application of 2 ml of PCL, gelatin, and PCL-gelatin (90:10 and 60:40) solution under the same deposition conditions. This was followed by application of 2 ml of PCL-gelatin solution under the same deposition conditions. At the conclusion of the study the animal was euthanized with a removal of blood in the heart.

Results and Discussion

In this study, we used solution blow spinning to fabricate conformal mats of PCL-gelatin mixed solution in situ using a commercial airbrush and compressed gas (Scheme 1). This technique allowed rapid conformal nanofiber deposition on any substrate.

Solutions comprised 6 wt% PCL and 6 wt% gelatin in TFE at a commercial compressor (Figure 1a-h). Analogous constraints of solution blow spinning, i.e., solution concentration, polymer molecular weight, solvent, and specific deposition conditions, are required for nanofiber generation. The key parameter for the resulting morphology of solution blow spinning is the concentration. The solution and deposition conditions that resulted in the rapid generation of uniform nanofibers were follows: 6 wt% gelatin only, 6 wt% PCL only, mixed PCL-gelatin (6:4 mass ratio), and mixed PCL-gelatin (9:1 mass ratio) in TFE with a commercialized compressor (Figure 1a-h).



Scheme 1: Schematic representation of solution blow spinning procedure being applied to a hepatic trauma.

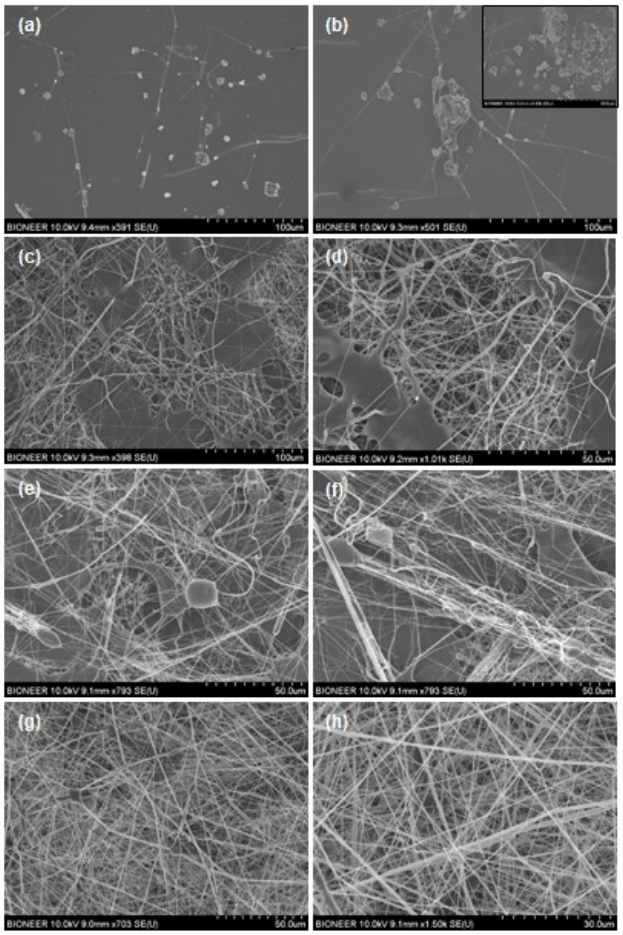


Figure 1: Scanning electron microscopy (SEM) micrographs of blow spun with different composition of gelatin and PCL; (a, b) 6 wt% gelatin in TFE, (c, d) 6 wt% PCL in TFE, (e, f) PCL-gelatin (60:40), and (g, h) PCL-gelatin (90:10).

The compatibility and interaction between PCL and gelatin molecules were characterized by FTIR spectroscopy. There is a hydrogen interaction between PCL and gelatin, which results in chain entanglement of the PCL and gelatin molecules [22]. As shown in Figure 2, PCL-related stretching modes are represented by the peaks at 2,943 cm^{-1} (asymmetric CH_2 stretching), 2,866 cm^{-1} (symmetric CH_2 stretching), 1,721 cm^{-1} (C=O stretching), 1,294 cm^{-1} (C-O and C-C stretching), and 1,240 cm^{-1} (asymmetric C-O-C stretching) [23]. The characteristic peaks of gelatin appear at approximately 1,650 cm^{-1} (amide I) and 1,540 cm^{-1} (amide II). With the increase in gelatin content, the relative intensities of the characteristic peaks of gelatin at 1,650 cm^{-1} and 1,540 cm^{-1} increased, as shown in the magnified curve. Shifting of the original absorption bands toward the lower wave numbers indicated that hydrogen bonds existed between PCL and gelatin.

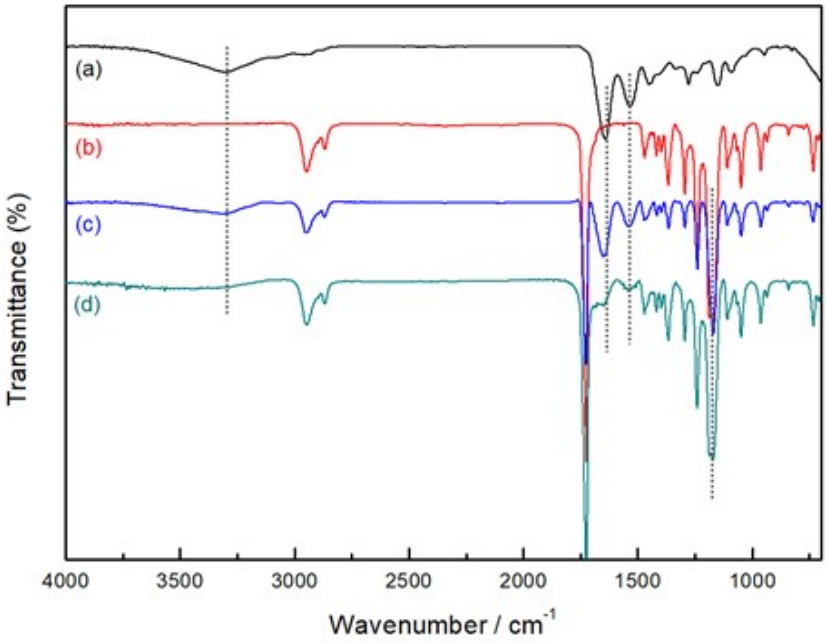


Figure 2: FT-IR (ATR mode) spectra of (a) 6 wt% gelatin in TFE, (b) 6 wt% PCL in TFE, (c) PCL-gelatin (60:40), and (d) PCL-gelatin (90:10). PCL-gelatin nanofibrous membranes with different PCL and gelatin composition.

TGA experiments were carried out on various samples, and the thermograms are shown in Figure 3 (A). The nanofiber membranes were observed to exhibit a thermal decomposition process with onset at around 180 °C for the gelatin film, 390 °C for the PCL nanofiber membrane, and 360 °C for PCL-gelatin (60:40), and 370 °C for PCL-gelatin (90:10).

The melting peak of PCL was observed to be 54 °C, while the gelatin was at 71 to 127 °C a broad range, as shown in the DSC thermograms (Figure 3 (B)). Besides the PCL and gelatin contents were diverse in different nanofiber, the endothermic melting enthalpy of PCL decreases with the increase of gelatin content. The thermogram of the PCL-gelatin nanofiber has an endothermic peak at about the 55 °C and 53 °C, as gelatin content increased the endothermic melting enthalpy of PCL decreases. In addition, because of the hydrogen bond and molecular chain entanglement between gelatin and PCL, the chain mobility and crystallization of PCL were restricted, which restrained the formation of PCL crystal stacks to some extent [50].

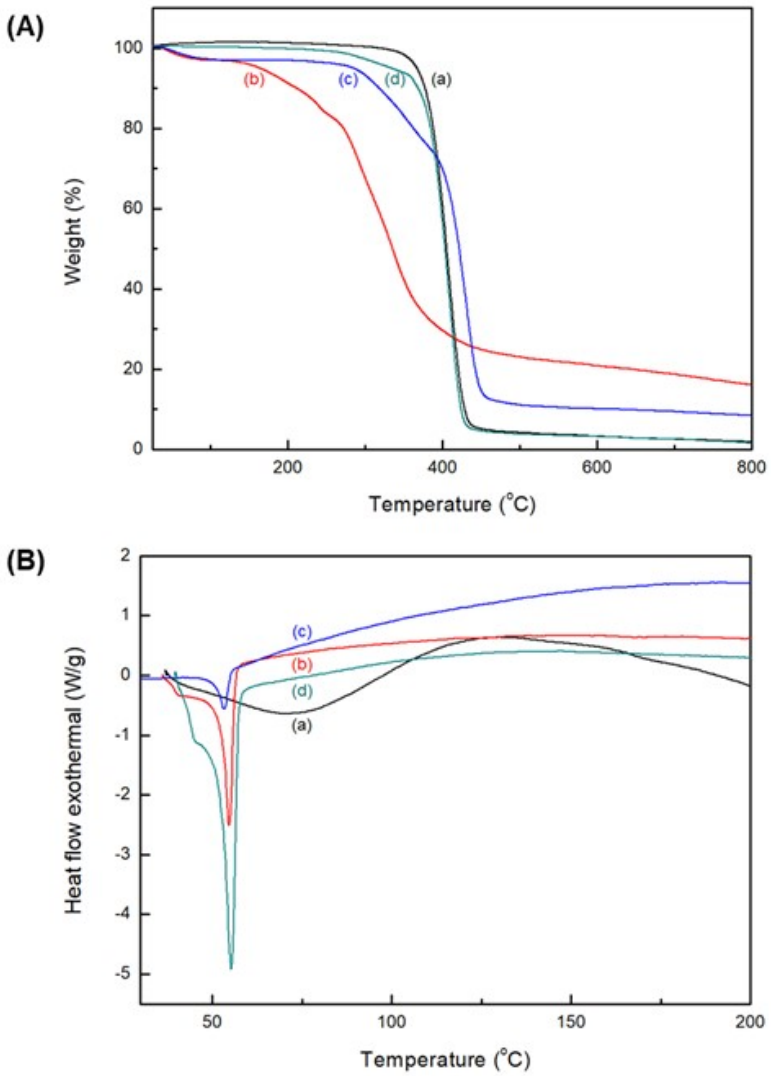


Figure 3: (A) TGA curves of (a) 6 wt% PCL in TFE, (b) 6 wt% gelatin in TFE, (c) PCL-gelatin (60:40), and (d) PCL-gelatin (90:10). (B) DSC thermograms of (a) 6 wt% gelatin in TFE, (b) 6 wt% PCL in TFE, (c) PCL-gelatin (60:40), and (d) PCL-gelatin (90:10). PCL-gelatin nanofibrous membranes with different PCL and gelatin composition. (Samples with a weight of approximately 5 mg were loaded in an aluminum crucible under dry conditions. The samples were cooled from 30 ℃ to and kept for 5 minutes, then heated to 200 ℃ under a nitrogen atmosphere at a heating rate of 10 ℃ min^{-1}).

The PCL-gelatin ratio had and obvious influence on the mechanical properties of the membranes (Supporting information, Figure S1). The strain and stress/MPa of the membranes increased with increasing PCL content. The high PCL content was favorable for the mechanical strength of the PCL-gelatin membranes. Thus, the tensile strength of the membranes with the PCL composition ratio increased. In addition, membranes at different PCL-gelatin ratios were all elastic, which is critical for surgical manipulation.

To illustrate potential future applications of solution blow spinning, we employed the technique to deposit nanofiber mats composed of PCL-gelatin (90:10) directly onto a mouse liver trauma model induced by a cauterization instrument, as depicted in Figure 4 (Video data of supporting information). In each instance, the deposition process yielded a uniform layer of nanofibers covering the liver defect in under 1 minute. Remarkably, the application of PCL-gelatin nanofibers effectively halted both liver hemorrhaging and the escape of air from the liver surface subsequent to segmentectomy.

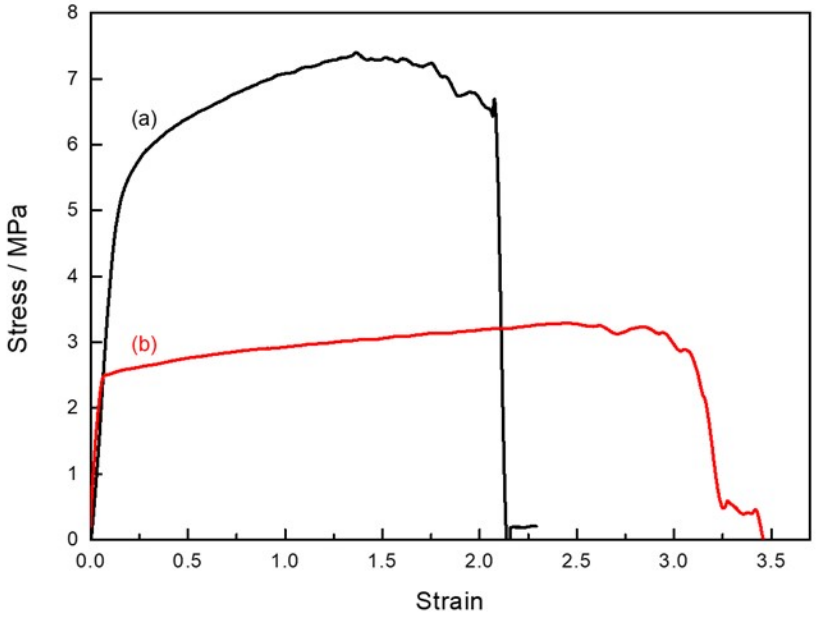


Figure S1: Stress-strain curves of blow spun PCL-gelatin nanofibrous membranes (a) 6 wt% PCL in TFE, and (b) PCL-gelatin (90:10).

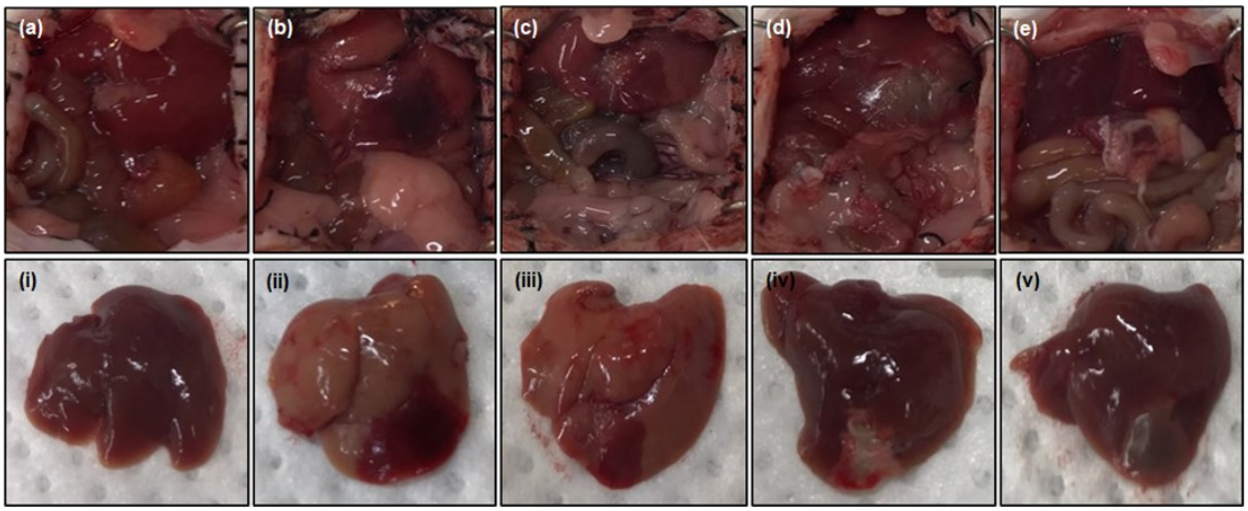


Figure 4: Images showing the direct deposition of conformal PCL-gelatin nanofibrous membranes liver injury (a-e) different composition of PCL and gelatin sealant after 3 days; (a) control (normal), (b) gelatin (6 wt%), (c) PCL (6 wt%), (d) PCL-gelatin (60:40), and (e) PCL-gelatin (90:10). (The below is the images after liver extraction).

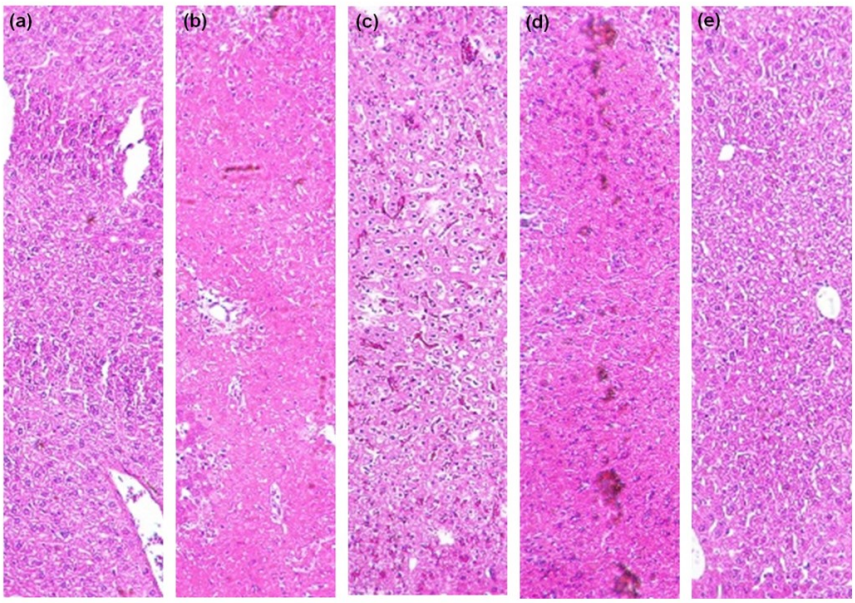


Figure 5: Histological micrographs with H&E staining of PCL-gelatin nanofibrous membranes with different PCL-gelatin ratio after direct deposition after 3 days; (a) control, (b) gelatin (6 wt%), (c) PCL (6 wt%), (d) PCL-gelatin (60:40), and (e) PCL-gelatin (90:10).

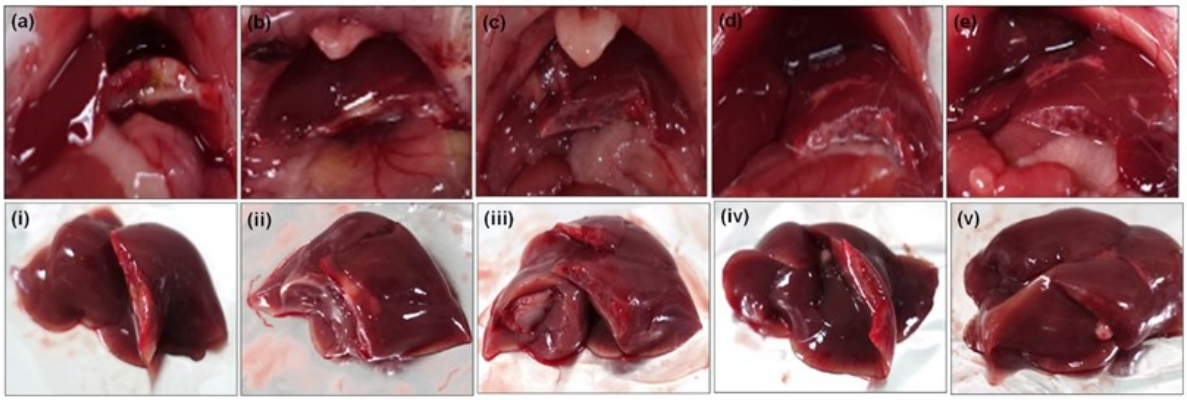


Figure S2: Images showing the direct deposition of conformal PCL-gelatin nanofibrous membranes liver injury (a-e) different composition of PCL and gelatin sealant after 3 days; (a) control, (b) gelatin (6 wt%), (c) PCL (6 wt%), (d) PCL-gelatin (60:40), and (e) PCL-gelatin (90:10). (The below is after enucleation).

Qualitative evaluation of the interaction of blood with the nanofiber membrane was performed using FE-SEM (Supporting information, Figure S3). After an hour of incubation and washing with PBS, significant platelet and erythrocyte adsorption onto the nanofiber matrix was observed. That shows, produce a more stable and definitive blood clotting between the hepatic trauma and PCL-gelatin nanofiber sheet for hemostatic [47].

The same injured liver mouse model was used in the 7 days survival study (Figure 6). As mentioned previously, the less than adequate subclinical number of nanofiber membranes used in this model resulted in a high incidence of liver injury. This injured liver is reflected in the enucleation-only control with a 50% (n = 10) mortality rate over the 7 days period, with almost all deaths occurring before day 3.

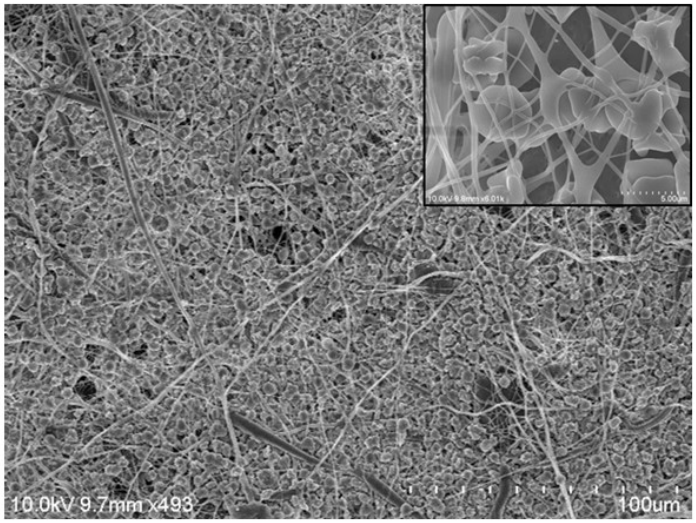


Figure S3: SEM of PCL-gelatin (90:10) nanofiber membrane incubated with citrated whole mouse blood. (Scale bar represents 100 μm (inset, 5 μm)).

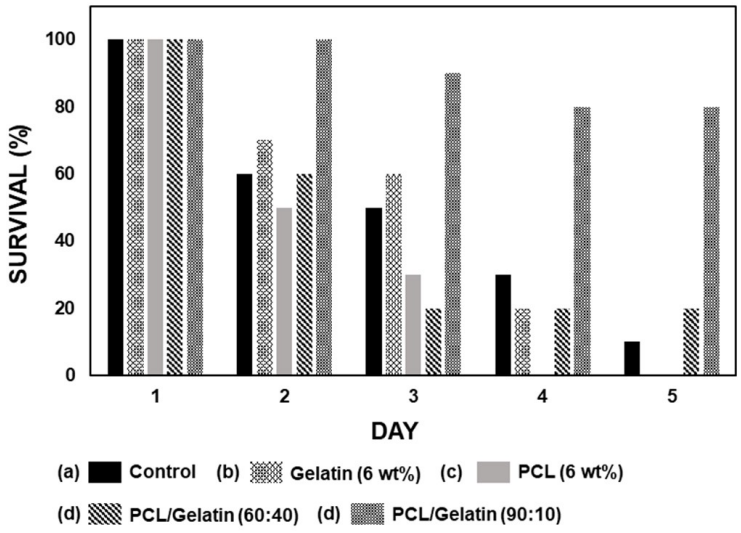


Figure 6: Survival study in case of liver injury.

Conclusion

Solution blow spinning offers an easily adaptable alternative that has the potential to generate on-demand conformal nanofiber mats directly on a wide range of targets. The present study demonstrates the facile fabrication of PCL-gelatin nanofibers using only a commercial airbrush and compressed gas. PCL content increased mechanical strength, and gelatin content enhanced cell adhesion, proliferation, and acceleration of the biodegradation rate. An animal study was then used to demonstrate some of the possible surgical applications, including use as a surgical hemostatic, surgical sealant, and tissue reconstruction.

Acknowledgement

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