

Research Article

Green Strategy to Develop Novel Drug-Containing Poly (ϵ -Caprolactone)-Chitosan-Silica Xerogel Hybrid Fibers for Biomedical Applications

Hua-Jian Zhou ¹, Shu-Hua Teng ¹, Yi-Bo Zhou ¹ and Hai-Sheng Qian ²

¹School of Materials Science and Physics, China University of Mining and Technology, Xuzhou 221116, China

²School of Biomedical Engineering, Anhui Medical University, Hefei 230032, China

Correspondence should be addressed to Shu-Hua Teng; shteng425@cumt.edu.cn and Hai-Sheng Qian; shqian@ahmu.edu.cn

Received 25 October 2020; Revised 7 December 2020; Accepted 15 December 2020; Published 24 December 2020

Academic Editor: Marcela Elisabeta Barbinta-Patrascu

Copyright © 2020 Hua-Jian Zhou et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

A facile and green method was explored to prepare the tetracycline hydrochloride- (TCH-) loaded poly (ϵ -caprolactone)-chitosan-silica xerogel (PCL-CS-SiO₂) hybrid fibers by using 90% acetic acid as a suitable solvent. The SEM results showed that those fibers exhibited a continuous, bead-free morphology, an average diameter of about 430 nm, and super-hydrophilicity ($\theta_{\text{water}} \approx 0^\circ$). The presence of SiO₂ was found to enhance the thermal stability of the hybrid fibers, and the actual content of SiO₂ was obtained by the TG measurement. Moreover, SiO₂ xerogel as an important bioceramic endowed the hybrid fibers with good drug release behavior and in vitro bioactivity, suggesting their potential use as novel drug carriers for bone tissue engineering. The present work is expected to offer a green strategy to develop novel, multifunctional hybrid materials.

1. Introduction

Micro- and nanofibers produced by electrospinning have been extensively used in tissue engineering, drug delivery, and some other biomedical fields due to their small size, good uniformity, high porosity, and large specific surface area [1–4]. Among the various electrospun biopolymers, poly (ϵ -caprolactone) (PCL) has attracted particular attention in terms of its good electrospinnability, mechanical strength, and biocompatibility [5–7]. Romos et al. prepared porous PCL microfibers at high relative humidity (65%) and explored the drug release behavior of the PCL fibers with different surface porosities [8]. However, when used as tissue engineering materials, the PCL fibers possess a poor hydrophilicity and lack bioactivity, which is unfavorable to the cell adhesion and tissue regeneration. To overcome those drawbacks, different kinds of PCL-based composite fibers have been developed by blending PCL with some other biocompatible inorganic or organic materials [9–12].

Chitosan (CS) as a natural polysaccharide exhibits excellent hydrophilicity and biological properties [13–15], but poor electrospinnability and weak mechanical strength. Silica

(SiO₂) xerogel is an important inorganic biomaterial having high mechanical properties, good bioactivity, and controlled drug release behavior [16, 17]. Therefore, it is desirable that the combination of PCL, CS, and SiO₂ would avoid their above-mentioned drawbacks and produce novel hybrid fibers with good morphology and multiple biofunctions. Ma et al. prepared the core-shell PCL/CS composite fibers through an emulsion electrospinning process [18]. Lee et al. formulated the PCL/SiO₂ hybrid sol into fibrous membranes by electrospinning for guided bone regeneration [19]. However, in order to obtain the bead-free PCL-based nanofibers, the researchers generally used some organic solvents (chloroform, dichloromethane, 1,1,1,3,3,3-hexafluoro-2-propanol, etc.) with more or less toxicity to the environment and human health. Moreover, there has been no relevant research on fabricating the tricomponent hybrid fibers of PCL-CS-SiO₂ for biomedical applications so far. Thus, green synthesis of the novel PCL-CS-SiO₂ fibers with improved hydrophilicity and biological performance is of great significance and urgency for the multiple bioapplications.

In this study, 90% acetic acid was used for the first time as a suitable green solvent to one-pot prepare the drug-

containing PCL-CS-SiO₂ hybrid fibers. The composition, morphology, and wettability of the hybrid fibers were characterized, and their drug release behavior was investigated to evaluate the feasibility as a novel drug carrier. In addition, their ability to form bone apatite *in vitro* was also assessed. The combination with SiO₂ xerogel would effectively improve the hydrophilicity and biological properties of the PCL-CS fibers while maintaining their good electrospinnability, thus generating PCL-CS-SiO₂ hybrid fibers with superior performance for multiple biomedical applications. Moreover, the present study would offer an effective pathway for the green synthesis of novel hybrid materials for various applications.

2. Experimental Procedure

2.1. Materials. Chitosan (CS) powder (medium molecular weight) was commercially obtained from Sigma-Aldrich Corporation (USA). Tetracycline hydrochloride (TCH) was purchased from Shanghai Macklin Biochemical Co. Ltd. (Shanghai, China). Poly (ϵ -caprolactone) (PCL) (Mn = 80,000), tetramethyl orthosilicate (TMOS), glacial acetic acid, and the other chemical reagents used in this study were supplied by Aladdin Industrial Co., Ltd. (Shanghai, China).

2.2. Preparation of the Drug-Containing PCL-CS-SiO₂ Hybrid Fibers. Firstly, PCL and CS powders were completely dissolved in 90% acetic acid to get a viscous solution containing 20% (*w/v*) PCL and 1.5% (*w/v*) CS, followed by the subsequent dissolution of TCH (4%, *w/v*). The silica sol was preobtained by fully hydrolyzing TMOS in distilled water under the catalysis of HCl (1 M). Then, the silica sol was slowly dropped into the above drug-containing PCL-CS solution and stirred for 2 h to form a homogeneous PCL-CS-SiO₂ hybrid sol containing 20 wt% SiO₂. For the electrospinning process, the PCL-CS-SiO₂ sol was injected into the 5 mL syringe with a 21 G needle and then electrospun at the electric voltage, flow rate, and spinneret-to-collector distance of 15 kV, 1 mL/h, and 15 cm, respectively. For comparison, the drug-free PCL-CS and PCL-CS-SiO₂ fibers as well as the drug-loaded PCL-CS fibers were also prepared using a similar procedure.

2.3. Characterizations of the Hybrid Fibers. The viscosity and conductivity of the solutions were measured by the rotational viscometer (Haake Viscotester C) and the conductivity meter (DDS-307), respectively. The wettability of the fibers was tested by the contact angle tester (JC2000D2A). The fiber morphology was investigated by using a SU8220 scanning electron microscope (SEM). The chemical groups of the fibers were identified with a PerkinElmer 983G Fourier transform infrared spectroscopy (FT-IR). In addition, the thermal behaviors of the fibers were characterized by STA 449 F3 Jupiter thermogravimetry/differential scanning calorimetry (TG/DSC).

2.4. Drug Release Behavior and In Vitro Bioactivity of the Hybrid Fibers. The drug release evaluation was performed by soaking the TCH-loaded fibers in 20 mL of the phosphate-

buffered saline (PBS) solution (pH 7.4, 0.01 M) at 37°C. At predetermined intervals, 5 mL supernatant was collected and tested using a UV-Vis spectrophotometer (Evolution 300) at 274 nm. The drug encapsulation efficiency of the samples was measured by immersing the drug-loaded fibrous membranes in the PBS solution for 24 h and then analyzing the concentration of the released drug in the supernatant by UV. The drug encapsulation efficiency was expressed as a percentage (%) of the actual drug loading amount divided by the theoretical drug amount contained in the fibers. In addition, the evaluation on the *in vitro* bioactivity of the PCL-CS-SiO₂ fibers was performed by immersing the fibrous membrane in simulate body fluid (SBF) for 3 days, after which the sample was rinsed with distilled water carefully, air-dried, and finally observed by SEM.

3. Results and Discussion

Conventionally, the CS fibers were usually prepared by using strong organic acids as the solvent, and the PCL fibers were generally obtained by using toxic organic solvents. To avoid the above problems, 90% acetic acid was used as a green solvent in our experiments to one-pot synthesize the TCH-containing PCL-CS-SiO₂ hybrid fibers. As illustrated in Figure 1, a viscous PCL-CS solution was firstly prepared, and then, TCH as a model drug was subsequently dissolved to get a clear yellow TCH-containing PCL-CS solution, followed by a thorough mixing with the SiO₂ sol. After such mixing, no precipitation or aggregation was observed, indicating the sufficient combination of the drug molecules with the PCL-CS-SiO₂ hybrid sol at a molecular level. Finally, the TCH-containing PCL-CS-SiO₂ hybrid sol was electrospun to form continuous fibers. The whole preparation process was green and facile. Moreover, the drug loading capacity of the hybrid fibers can be adjusted by simply changing the TCH amount added.

Figure 2 shows the SEM images of the different fibers. It was revealed in Figure 2(a) that the PCL-CS fibers coexisted with many beads and droplets, which was mainly attributable to the relatively high viscosity but low conductivity of the PCL-CS solution (Table 1). After TCH was loaded, the viscosity of the PCL-CS solution was greatly decreased to 620 mPa·s while the conductivity was increased to 354 μ S/cm. As a result, the electrospinnability of the PCL-CS solution was significantly improved, eventually producing a bead-free morphology and an average fiber diameter of about 290 nm (Figure 2(b)). Such morphology was very similar to that of the PCL-based composite fibers reported by Miele et al. [20].

As exhibited in Figure 2(c), a further mixing of the TCH-containing PCL-CS solution with the SiO₂ sol generated continuous and defect-free hybrid fibers having a mean diameter of approximately 430 nm. By comparing Figures 2(b) and 2(c), it was suggested that, even though the drug-loaded PCL-CS-SiO₂ hybrid fibers displayed an increased average diameter and a wider diameter distribution than the PCL-CS equivalents, they presented an obvious improvement in the continuity and dispersity of the fibers probably due to the increase of the conductivity.

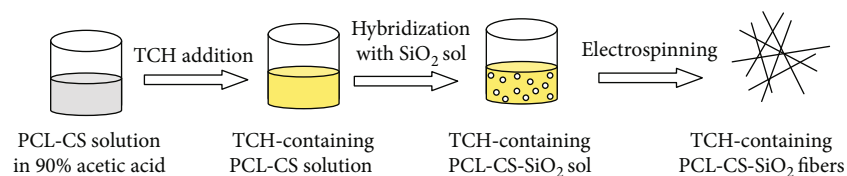


FIGURE 1: Schematic illustration showing the facile preparation process of the PCL-CS-SiO₂ hybrid fibers.

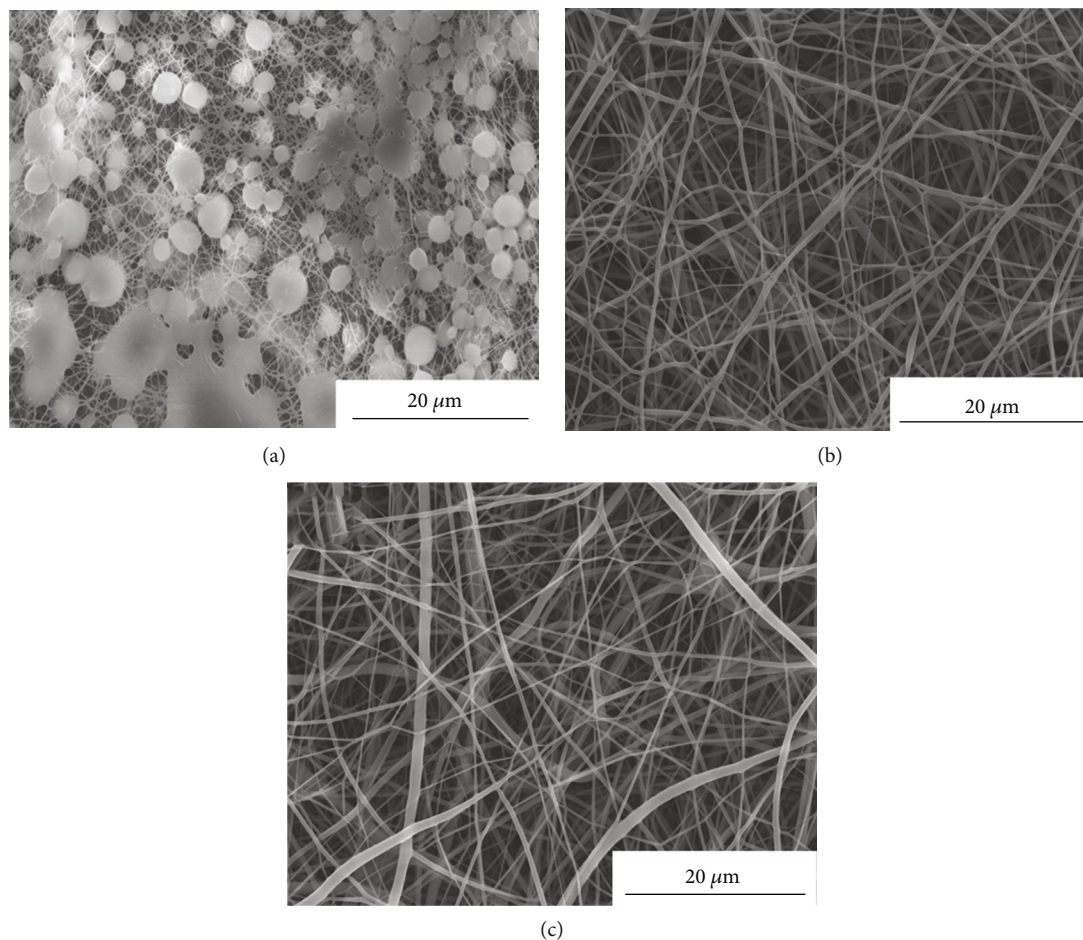


FIGURE 2: SEM images of (a) PCL-CS, (b) drug-loaded PCL-CS, and (c) drug-loaded PCL-CS-SiO₂ fibers.

TABLE 1: Viscosity, conductivity, and contact angles of different fibers.

Samples	Viscosity (mPa·s)	Conductivity ($\mu\text{S}/\text{cm}$)	Contact angle ($^\circ$)	Drug entrapment efficiency (%)
PCL-CS	1535 ± 24	33 ± 4	122.6 ± 10.1	—
Drug-loaded PCL-CS	620 ± 17	354 ± 10	43.2 ± 5.7	94.0 ± 1.3
Drug-loaded PCL-CS-SiO ₂	349 ± 6	367 ± 15	~ 0	96.4 ± 0.8

In addition, the hydrophilicity of the PCL-CS fibers was also significantly enhanced by the addition of TCH and SiO₂. Particularly, the contact angle of water on the drug-loaded PCL-CS hybrid fibers decreased to nearly zero after combination with the SiO₂ sol.

The FT-IR spectra of three samples were shown in Figure 3(a). The absorption peaks between 2800 and 3000 cm^{-1} corresponded to the C-H stretching vibrations of the PCL and CS molecules [21]. The strong peaks around 1732 and 1175 cm^{-1} were assigned to the C=O and C-O-C

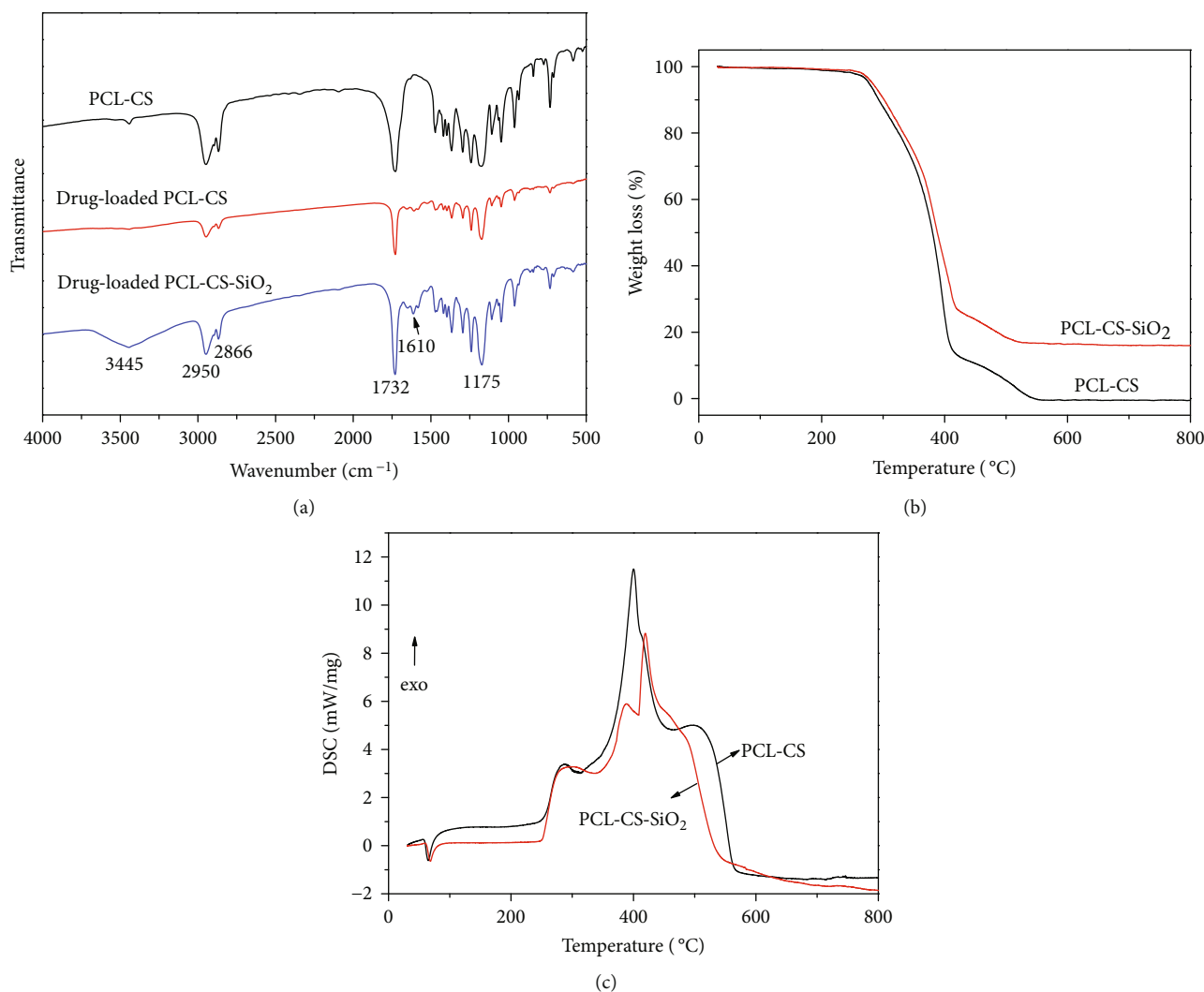


FIGURE 3: (a) FT-IR spectra, (b) TG curves, and (c) DSC profiles of different samples.

stretching vibrations of PCL, respectively [22]. In the spectra of the drug-loaded PCL-CS and PCL-CS-SiO₂ fibers, TCH exhibited a characteristic absorption peak of the C=C groups at 1610 cm⁻¹. It was also found that the weak adsorption peak at 3300-3600 cm⁻¹ became stronger and wider after combination with SiO₂ probably due to the abundant presence of the Si-OH groups in silica xerogel [23].

The presence of silica xerogel could be further confirmed by TG/DSC. As depicted in Figures 3(b) and 3(c), the sharp weight loss between 300°C and 550°C was mainly related to the decomposition of PCL and CS together with a polycondensation process of the SiO₂ xerogel [24]. The appearance of the new exothermic peak located at about 390°C in the DSC profile of the PCL-CS-SiO₂ fibers was probably indicative of the successful combination of PCL-CS with silica xerogel. The shift of the exothermic peak of the PCL-CS fibers at 400°C to a higher temperature implied the increase of their thermal stability by incorporating SiO₂ xerogel. In addition, the actual content of SiO₂ contained in the PCL-CS-SiO₂ hybrid fibers was calculated from the TG curve to be 15.8%, slightly lower than its theoretical value (20%).

It was revealed in Table 1 that the PCL-CS-SiO₂ fibers exhibited a higher drug entrapment efficiency (96.4%) than the PCL-CS fibers (94.0%), which was probably attributable to the strong adsorption ability of the SiO₂ xerogel to the TCH molecules by virtue of its abundant -OH groups [25, 26]. The cumulative TCH release profiles of the drug-loaded fibers were depicted in Figure 4(a). Within the first 1 h, both samples displayed a burst drug release due to their highly hydrophilic nature. As shown in the inset of Figure 4(a), about 91.6% and 77.5% of TCH were released during this period from the PCL-CS and PCL-CS-SiO₂ fibers, respectively. Subsequently, the drug release rate slowed down and the PCL-CS-SiO₂ hybrid fibers exhibited a more sustained release behavior than the PCL-CS fibers, which can be attributed to their good fiber morphology and the formation of the three-dimensional network by the combination of PCL-CS with SiO₂ sol. After 24 h of testing, the cumulative amount of TCH released from the PCL-CS and PCL-CS-SiO₂ fibers reached about 95.3% and 97.2%, respectively.

In addition, it was revealed from Figure 4(b) that the PCL-CS-SiO₂ hybrid fibers possessed a good in vitro

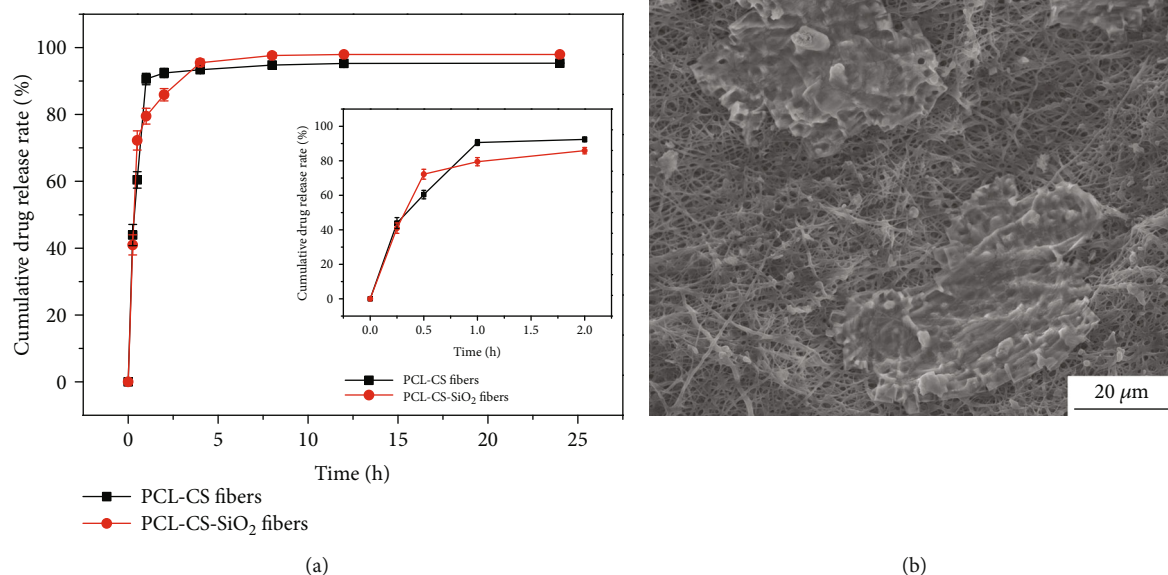


FIGURE 4: (a) Drug release profiles of the PCL-CS and PCL-CS-SiO₂ fibers and (b) SEM image of the PCL-CS-SiO₂ fibers after immersion in the SBF solution for 3 days.

bioactivity. After immersion in the SBF solution for 3 days, some particle aggregates were found to precipitate on the surface of the fibrous membrane, with a typical morphology of the bone-like apatite particles formed on the SiO₂-related materials [27, 28]. In the PCL-CS-SiO₂ hybrid fibers, SiO₂ xerogel as a well-known bioactive ceramic was homogeneously incorporated into the PCL-CS matrix, which was beneficial to improve the drug release behavior and in vitro bioactivity of the hybrid fibers. Furthermore, even though the fibers were immersed in SBF for 3 days, they still presented an intact morphology without obvious fiber integration or degradation, suggesting their good stability in aqueous system.

4. Conclusions

Novel drug-containing PCL-CS-SiO₂ hybrid fibers were facilely synthesized by using nontoxic acetic acid (90%) as a suitable solvent. The SEM results revealed that the continuous and dispersed hybrid fibers were generated, with an average diameter of about 430 nm. The chemical compositions of the hybrid fibers were identified by TG and FT-IR analysis. Moreover, the drug-loaded PCL-CS-SiO₂ hybrid fibers exhibited super-hydrophilicity ($\theta_{\text{water}} \approx 0^\circ$) and a drug entrapment efficiency of about 96.4%. In addition, they possessed a good in vitro bioactivity and an improved drug release performance as compared with the PCL-CS fibers, which makes them more suitable to serve as a novel drug carrier for bone tissue engineering than the PCL-CS fibers.

Data Availability

The data used to support the findings of this study are included within the article. Any more specific details in the data will be delivered by the corresponding authors upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

This work was financially supported by the Fundamental Research Funds for the Central Universities (No. 2019XKQYMS09).

References

- [1] J. Xue, T. Wu, Y. Dai, and Y. Xia, "Electrospinning and electrospun nanofibers: methods, materials, and applications," *Chemical Reviews*, vol. 119, no. 8, pp. 5298–5415, 2019.
- [2] R. Johnson, Y. Ding, N. Nagiah, E. Monnet, and W. Tan, "Coaxially-structured fibres with tailored material properties for vascular graft implant," *Materials Science and Engineering C*, vol. 97, pp. 1–11, 2019.
- [3] R. M. D. Soares, N. M. Siqueira, M. P. Prabhakaram, and S. Ramakrishna, "Electrospinning and electrospray of bio-based and natural polymers for biomaterials development," *Materials Science and Engineering C*, vol. 92, pp. 969–982, 2018.
- [4] F. D. Wang, S. Hu, Q. X. Jia, and L. Q. Zhang, "Advances in electrospinning of natural biomaterials for wound dressing," *Journal of Nanomaterials*, vol. 2020, Article ID 8719859, 14 pages, 2020.
- [5] J. Fernández-Pérez, K. E. Kador, A. P. Lynch, and M. Ahearne, "Characterization of extracellular matrix modified poly(ϵ -caprolactone) electrospun scaffolds with differing fiber orientations for corneal stroma regeneration," *Materials Science and Engineering C*, vol. 108, article 110415, 2020.
- [6] H. Yu, Y. T. Jia, G. Z. Chen, and Y. M. Zhang, "Fabrication of core/sheath PCL/PEG-PNIPAAm fibers as thermosensitive release carriers by a new technique combining blend electrospinning and ultraviolet-induced graft polymerization," *Materials Letters*, vol. 164, pp. 505–508, 2016.

- [7] S. Salerno, F. Tasselli, E. Drioli, and L. De Bartolo, "Poly(epsilon-caprolactone) hollow fiber membranes for the biofabrication of a vascularized human liver tissue," *Membranes*, vol. 10, article 112, 2020.
- [8] C. Romos, G. M. Lanno, I. Laidmäe, A. Meos, R. Härmas, and K. Kogermann, "High humidity electrospinning of porous fibers for tuning the release of drug delivery systems," *International Journal of Polymeric Materials and Polymeric Biomaterials*, pp. 1–13, 2020.
- [9] A. Leones, A. Mujica-Garcia, M. P. Arrieta et al., "Organic and inorganic PCL-based electrospun fibers," *Polymers*, vol. 12, article 1325, 2020.
- [10] Q. Q. Sang, H. Y. Li, G. Williams, H. L. Wu, and L. M. Zhu, "Core-shell poly(lactide-co-epsilon-caprolactone)-gelatin fiber scaffolds as pH-sensitive drug delivery systems," *Journal of Biomaterials Applications*, vol. 32, no. 8, pp. 1105–1118, 2018.
- [11] Ş. M. Eskitoros-Togay, Y. E. Bulbul, and N. Dilsiz, "Controlled release of doxycycline within core/shell poly(epsilon-caprolactone)/poly(ethylene oxide) fibers via coaxial electrospinning," *Journal of Applied Polymer Science*, vol. 137, article e49273, 2020.
- [12] J. H. Si, Z. X. Cui, Q. T. Wang, Q. Liu, and C. T. Liu, "Biomimetic composite scaffolds based on mineralization of hydroxyapatite on electrospun poly(epsilon-caprolactone)/nanocellulose fibers," *Carbohydrate Polymers*, vol. 143, pp. 270–278, 2016.
- [13] M. Dash, F. Chiellini, R. M. Ottenbrite, and E. Chiellini, "Chitosan—a versatile semi-synthetic polymer in biomedical applications," *Progress in Polymer Science*, vol. 36, no. 8, pp. 981–1014, 2011.
- [14] K. Y. Yin, P. Divakar, and U. G. K. Wegst, "Plant-derived nanocellulose as structural and mechanical reinforcement of freeze-cast chitosan scaffolds for biomedical applications," *Biomacromolecules*, vol. 20, no. 10, pp. 3733–3745, 2019.
- [15] H. Sun, D. Choi, J. Heo, S. Y. Jung, and J. Hong, "Studies on the drug loading and release profiles of degradable chitosan-based multilayer films for anticancer treatment," *Cancers*, vol. 12, p. 593, 2020.
- [16] S. H. Jun, E. J. Lee, S. W. Yook, H. E. Kim, H. W. Kim, and Y. H. Koh, "A bioactive coating of a silica xerogel/chitosan hybrid on titanium by a room temperature sol-gel process," *Acta Biomaterialia*, vol. 6, no. 1, pp. 302–307, 2010.
- [17] J.-S. Oh and E.-J. Lee, "Engineered dressing of hybrid chitosan-silica for effective delivery of keratin growth factor and acceleration of wound healing," *Materials Science and Engineering C*, vol. 103, article 109815, 2019.
- [18] L. Ma, X. J. Shi, X. X. Zhang, and L. L. Li, "Electrospinning of polycaprolacton/chitosan core-shell nanofibers by a stable emulsion system," *Colloids and Surfaces A*, vol. 583, article 123956, 2019.
- [19] E.-J. Lee, S.-H. Teng, T.-S. Jang et al., "Nanostructured poly(epsilon-caprolactone)-silica xerogel fibrous membrane for guided bone regeneration," *Acta Biomaterialia*, vol. 6, no. 9, pp. 3557–3565, 2010.
- [20] D. Miele, L. Catenacci, S. Rossi et al., "Collagen/PCL nanofibers electrospun in green solvent by DOE assisted process. An insight into collagen contribution," *Materials*, vol. 13, p. 4698, 2020.
- [21] Y. Huang, N. Dan, W. Dan, and W. Zhao, "Reinforcement of polycaprolactone/chitosan with nanoclay and controlled release of curcumin for wound dressing," *ACS Omega*, vol. 4, no. 27, pp. 22292–22301, 2019.
- [22] B. Liu, T. Yao, L. Ren, Y. Zhao, and X. Yuan, "Antibacterial PCL electrospun membranes containing synthetic polypeptides for biomedical purposes," *Colloids and Surfaces B*, vol. 172, pp. 330–337, 2018.
- [23] T. Pirzada, S. A. Arvidson, C. D. Saquing, S. S. Shah, and S. A. Khan, "Hybrid carbon silica nanofibers through sol-gel electrospinning," *Langmuir*, vol. 30, no. 51, pp. 15504–15513, 2014.
- [24] S.-H. Teng, N. Niu, F.-W. Chen, and P. Wang, "Polyvinyl alcohol/silica hybrid microspheres: synthesis, characterization and potential applications as adsorbents," *Materials Research Express*, vol. 6, no. 5, article 055201, 2019.
- [25] H. S. Jamwal and G. S. Chauhan, "Designing silica-based hybrid polymers and their application in the loading and release of fluorescein as a model drug and diagnostic agent," *Advance Polymer Technology*, vol. 37, no. 2, pp. 411–418, 2018.
- [26] M. Prokopowicz, "Correlation between physicochemical properties of doxorubicin-loaded silica/polydimethylsiloxane xerogel and *in vitro* release of drug," *Acta Biomaterialia*, vol. 5, no. 1, pp. 193–207, 2009.
- [27] B. H. Yoon, H. E. Kim, and H. W. Kim, "Bioactive microspheres produced from gelatin-siloxane hybrids for bone regeneration," *Journal of Materials Science-Materials in Medicine*, vol. 19, no. 6, pp. 2287–2292, 2008.
- [28] N. Niu, S.-H. Teng, H.-J. Zhou, and H.-S. Qian, "Synthesis, characterization, and *in vitro* drug delivery of chitosan-silica hybrid microspheres for bone tissue engineering," *Journal of Nanomaterials*, vol. 2019, Article ID 7425787, 2019.