



Scaffold composed of porous vancomycin-loaded poly(lactide-co-glycolide) microspheres: A controlled-release drug delivery system with shape-memory effect



Lin Du ^{a,b}, Shenyu Yang ^{a,b}, Wenqiang Li ^{a,b}, Haoying Li ^{a,b}, Shanbao Feng ^{a,b}, Rong Zeng ^{a,b}, Bin Yu ^c, Liangxing Xiao ^c, Heng-Yong Nie ^{d,e}, Mei Tu ^{a,b,*}

^a Department of Materials Science and Technology, Jinan University, Guangzhou, Guangdong 510632, China

^b Engineering Research Center of Artificial Organs and Materials, Ministry of Education, Jinan University, Guangzhou, Guangdong 510632, China

^c Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong 510515, China

^d Surface Science Western, The University of Western Ontario, 999 Collip Circle, London, Ontario N6G 0J3, Canada

^e Department of Physics and Astronomy, The University of Western Ontario, London, Ontario N6A 3K7, Canada

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ABSTRACT

Loading antibiotics in a biodegradable polymer matrix is an excellent way to control its release kinetics, which eliminates side effects caused by conventional administrations of the drug. This approach is especially beneficial for bone regeneration when using a scaffold made of a biodegradable polymer loaded with drug agents capable of controllable releases. In this case, the scaffold serves as a mechanical support to tissue formation and the drug agents may provide biomolecules to assist the tissue formation and/or provide antibiotics to prevent tissues from infections. Towards this goal, we have developed an approach to make vancomycin-loaded poly(lactide-co-glycolide) (PLGA) microspheres, from which we made scaffolds by compression molding. In this article we concentrate on characterizing the porosity and drug release profiles, as well as verifying shape-memory effect of the scaffolds. The scaffold was biodegradable and showed a much slower drug release profile than microspheres. We confirmed that our PLGA scaffolds recovered to their permanent shapes when heated to 45 °C. We believe that these scaffolds will find applications in bone regeneration where both the use of antibiotics against infection and accommodation to spatial restrictions may be required.

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1. Introduction

Glycopeptides are widely administered as an injectable drug agent into the human body. For example, vancomycin is a tricyclic glycopeptide antibiotic effective against Gram-positive bacteria and is commonly used to prevent and treat infections caused by *Staphylococcus aureus* [1, 2]. However, these drug agents are usually easily hydrolyzed and removed from the body, thus requiring perhaps daily injections. In order to address these difficulties encountered with traditional methods of administration, controlled-release drug delivery systems are being developed rapidly [3–6]. To reduce the number of injections and to avoid long-term large doses, which cause side effects such as renal toxicity and ototoxicity, the need for controlled release of vancomycin-containing systems is required to alleviate the suffering of patients. Use of biodegradable polymer as a carrier (matrix) for drug agents has

been identified as an excellent controlled-release drug delivery system, which is under intensive research in the chemical research community and pharmaceutical industry [6,7]. Among the biodegradable polymers, poly(lactide-co-glycolide) (PLGA) is a popular choice because it is approved by the U.S. Food and Drug Administration and can have its biodegradability tailored by way of adjusting the ratio between the lactide and glycolide moieties [8–10].

Drug-containing PLGA systems include microspheres [5,11] and scaffolds [9,12–14], both of which have been used for tissue engineering. The scaffold approach is especially suitable for bone regeneration. An ideal scaffold designed for such purposes should meet the following requirements: (a) blood vessels must form through the scaffold so as to sustain osteogenesis by supporting nutrient, oxygen and waste transport and (b) the scaffold should degrade within a specified time in vivo, making space for the grown tissue to take over [12]. Therefore, the porosity of scaffold is vitally important in bone regeneration [15, 16]. Porous materials [17–21] have been pursued for more than four decades. Methodology development for construction of porous scaffold having appropriate pore scales [16] for intended applications is still in the forefront of tissue regeneration. There are excellent reviews on

* Corresponding author at: Department of Material Science and Engineering, College of Science and Engineering, Jinan University, 601 Huangpu Avenue West, Guangzhou, Guangdong 510632, China.

E-mail address: tumei@jnu.edu.cn (M. Tu).

applications of porous scaffolds used in tissue engineering [12,22,23]. The important factors of scaffold include its mechanical strength and degradation rates [23]. Scaffold loaded with antibiotics for preventing injured bones from infection prevention is beneficial for tissue engineering [6].

We have developed porous vancomycin-containing PLGA microspheres as a controlled drug release system and carried out research work on controlling the size and porosity, as well as encapsulation efficiency of the microspheres [24]. In this article, we concentrate on preparing porous scaffolds by compression molding of porous microspheres loaded with antibiotics (vancomycin) and characterizing their porosity and drug release kinetics. Beside biocompatibility and degradability, some special implants need to be able to transform their shape and volume after they are subjected to external stimuli. Shape-memory polymers [25,26] fulfill this requirement [27] because the temporary shape of a polymer object designed for an initial installation returns to its permanent shape upon a stimulus such as temperature, light, electric current and even water [28]. Therefore, extensive efforts have been put in designing/synthesizing various shape-memory soft materials [29–32] and development of their biomedical applications [28]. We demonstrate that our scaffolds made of vancomycin-loaded, porous PLGA microspheres possess shape-memory effect, which makes this controlled-release drug delivery system a promising approach to tissue engineering with measures to prevent tissue infection.

2. Materials and methods

2.1. Chemicals

The drug agents used in this work were vancomycin (Zhejiang Medicine, Xinchang, China) and vancomycin-rhodamine B (Nanfang Hospital, Southern Medical University, China). The polymer carrier used to build microspheres was copolymer poly(D, L-lactide-co-glycolide) (D, L-lactide: glycolide 50:50, $M_w = 30,000$, Shenzhen Polymtek Biomaterial, China). The glass transition temperature (T_g) of this PLGA was approximately 42 °C as determined using differential scanning calorimetry (Q20, TA Instruments, USA). Also used in the preparation processes for the drug-loaded microspheres were chemicals including dichloromethane, absolute ethanol, glycerin (Titan, China), decaglycerol dioleate (Jinan Dowin Chemical Technology, China) and Span® 80 (Dongying Fengxiang, China).

2.2. Preparation of porous microspheres

Fig. 1 shows a schematic illustration for the preparation of vancomycin-loaded PLGA porous microspheres by the Poiseuille flow approach. A solution of 50 mg vancomycin (internal aqueous phase, denoted as W) in 1 mL de-ionized water was added to a solution containing 500 mg PLGA in 5 mL dichloromethane (oil phase, O), followed by the addition of Span® 80. As shown in Fig. 1, this water/oil (W/O) emulsion was injected to a coagulating bath (composed of absolute ethanol, glycerin and decaglycerol dioleate) via a 20-mL syringe fixed on an injection pump. The emulsion was mixed with the bath with a stirring rod. This Poiseuille flow resulted in viscous liquid, within which microspheres were dispersed in the coagulating bath. Then, this viscous liquid was

washed repeatedly with absolute ethanol until precipitates (i.e., microspheres) appeared. The microspheres were finally rinsed using deionized water to remove residual ethanol. The final product was obtained by freeze-drying the microspheres at -40 °C.

In order to examine the impact of absolute ethanol, glycerin and decaglycerol dioleate in a coagulating bath on the formation of porous microspheres, we made microsphere samples A_1 – A_5 in five coagulating baths composed of different volume/volume (v/v) % concentrations of the three ingredients as detailed in Table 1. Details about the impact on the formation of porous microspheres will be discussed later.

2.3. Scaffolds prepared using vancomycin-loaded PLGA microspheres

Scaffolds were made by compressing vancomycin-loaded PLGA porous microspheres (prepared under the coagulating bath A_2) into four different molds of (a) an I-shape (i.e., cylindrical), (b) a J-shape, (c) an N-shape and (d) a U-shape, all of which had a length of 30 mm and a diameter in the range of 2.5–4.8 mm. The molds were heated to 37 °C, which was slightly lower than T_g of PLGA (42 °C), for sintering for 30 min until the microspheres were heated uniformly without cracking. Then the molds were heated to 45 °C for 2 h to achieve bonding between microspheres. The fabrication process is illustrated in Fig. 2. After the molds were cooled to the room temperature the scaffolds were removed from the molds.

2.4. Characterizations of microspheres and scaffolds

The surface of porous microspheres and scaffolds was examined using a scanning electron microscope (SEM) (LEO1530VP, Zeiss, Germany). Samples of microspheres and scaffolds were sputter coated with gold to prevent charging. SEM was used to examine the internal structure of scaffold on cross section of an I-shape scaffold freeze-fractured after the scaffold was immersed in liquid nitrogen for 5 min. In order to determine the presence of vancomycin in the porous microspheres, we used vancomycin-rhodamine B to make a sample of microspheres so as to use confocal laser scanning microscope (CLSM) (LEXT OLS4100, Olympus, Japan) to image the tracer rhodamine B via its fluorescence.

2.5. Vancomycin release profiles

A solution containing 30–40 mg microspheres in 2 mL dichloromethane was made, into which 2 mL PBS (0.1 M, pH 7.4) was added after a 2-h waiting time. The solution was set for 6 h following a rigorous mixing. Then the supernatant was transferred into a test tube, where 2 mL PBS was added. This process was repeated three times to extract vancomycin fully. The concentration of vancomycin in an aqueous solution was determined using an ultraviolet spectrophotometer (UV-8000, Metash Instruments, China) operated at wavelength $\lambda = 281$ nm (this technique was used to determine vancomycin concentrations for all samples). The actual oligonucleotide loading, termed as vancomycin encapsulation, has been reported elsewhere [24].

Microspheres of sample A_2 (30–40 mg) and a scaffold (I-shaped with a length of 30 mm) made using sample A_2 were placed separately in different centrifuge tubes containing 30 mL PBS (0.1 M, pH 7.4). The

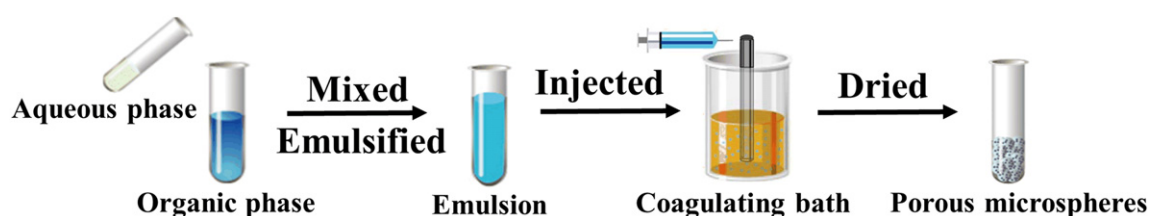


Fig. 1. Schematic illustration of the preparation of porous vancomycin-loaded PLGA microspheres.

Table 1
Different coagulating baths used for preparation of porous microspheres samples A₁–A₅.

Sample	Absolute ethanol (v/v %)	Glycerin (v/v %)	Decaglyceryl dioleate (v/v %)
A ₁	34	64	2
A ₂	23	75	2
A ₃	18	80	2
A ₄	16	82	2
A ₅	25	75	0

tubes were then kept in a thermostat incubator (THZ-103B, Shanghai Yiheng Instruments, China) that was maintained at 37 °C and vibrated at a frequency of 100 cycles/min. At predetermined time intervals, 1 mL of solution was taken out from the tube for estimation of vancomycin release profile and 1-mL fresh PBS was added to the tube.

2.6. Shape-memory effect of scaffolds prepared using vancomycin-loaded PLGA microspheres

A porous microspheres-based scaffold with an initial I-shape was first folded into a temporary U-shape after the scaffold was heated at 45 °C for approximately 5 min. Then the U-shaped scaffold was cooled down to 4 °C in a refrigerator (this stage usually took 15 min). Finally, this U-shape scaffold was put into a thermostat incubator (DZF-6022, Shanghai Yiheng Instruments, China) maintained at 45 °C until the scaffold recovered to its initial I-shape. We also repeated the shape memory experiment for scaffolds with initial J-, N-, and U-shapes by first rendering them a temporary I-shape followed by recovering them to their initial shapes at 45 °C.

3. Results and discussion

3.1. Characterizations of microspheres and scaffolds

Shown in Fig. 3a–e are SEM images of microspheres A₁–A₅, respectively, which were prepared from the five different coagulating baths with different concentrations of the solvents consisting of the coagulating solution. Fig. 3a shows the SEM image of the product (i.e., A₁) obtained from the coagulating bath containing 34% (v/v) ethanol, 64% glycerin and 2% decaglyceryl dioleate. Ethanol in the coagulating bath serves as the antisolvent for dichloromethane in the vancomycin-loaded PLGA emulsion. High concentration ethanol solidifies PLGA before the emulsion is rendered spherical droplets by the stirred coagulating bath. The emulsion is thus solidified into irregular shapes as seen in Fig. 3a above this critical concentration of absolute ethanol. The irregular shape shown in Fig. 3a is most likely a result of a PLGA skin, which is surrounded by high concentration levels of antisolvent ethanol and rapidly forms before all dichloromethane and de-ionized water leave the core of emulsion droplets.

When the ethanol concentration is decreased to 23%, as shown in Fig. 3b, porous microspheres (A₂) are obtained. Fig. 3c shows a representative microsphere (A₃) obtained when further decreasing the ethanol concentration in the coagulating bath to 18%. Microsphere A₂

appears to have fewer and larger pores, as well as a rougher surface than A₃. When the ethanol concentration is decreased to 16%, as shown in Fig. 3d, the pores of the microsphere A₄ are vanishing and its surface becomes uneven. This experimental observation clarified the importance of the antisolvent (i.e., ethanol) in the stirred coagulating bath on solidifying the vancomycin-loaded PLGA emulsion into uniform microspheres. A balance between the antisolvent and glycerin in the coagulating bath is thus important in determining the smoothness and the porosity of the microspheres prepared.

Shown in Fig. 3e is a representative microsphere A₅ obtained from a coagulating bath containing 25% ethanol and 75% glycerin without the presence of decaglyceryl dioleate. There are no pores at all present on the surface of the microsphere. This observation verifies that the pores observed on microspheres shown in Fig. 3b and c (prepared in coagulating baths with 2% decaglyceryl dioleate, respectively) are caused by decaglyceryl dioleate, which is a polyglycerol fatty acid ester acting as a porogen. Polyglycerol fatty acid esters have been known to be associated with the formation of porous polymer microparticles [33]. Small drops of decaglyceryl dioleate are adsorbed at the emulsion droplets. The mechanism of formation of porous microspheres is that small drops of decaglyceryl dioleate are adsorbed on and swell into the emulsion droplets that are the precursors of microspheres. Then drops of decaglyceryl dioleate expand to form a cubic phase via adsorption of liquids in the coagulating bath [34,35]. After droplets of emulsion are solidified and drops of decaglyceryl dioleate are removed by ethanol rinse, porous microspheres are obtained.

By taking advantage of the fluorescence emitted from rhodamine B nanoparticles, we prepared PLGA microspheres loaded with vancomycin-rhodamine B nanoparticles for the use of CLSM to determine the distribution of the drug agent in the polymer microsphere. Fig. 3f shows a CLSM image representing the fluorescence of rhodamine B nanoparticles for microspheres. The strength of CLSM lies in its ability to image the object at different depths. Therefore, this imaging technique is capable of examination of the distribution of the drug agent through the depth of a polymer matrix [36,37]. In Fig. 3f, the fluorescence signals represent vancomycin-rhodamine B nanoparticles in the PLGA microspheres. From this image, we verify that the vancomycin-rhodamine B nanoparticles are homogeneously distributed in the microspheres. We also collected images at different depths and confirmed that every layer probed showed the presence of vancomycin-rhodamine B.

A photograph of an I-shape scaffold made of porous microspheres is shown in Fig. 3g. The SEM images of a freeze-fractured cross section imaged at two different magnifications are displayed in Fig. 3h and i. The SEM images depict that the compressed microspheres in the scaffold still largely maintain their spherical shape [38]. The contacting portions of the adjacent microspheres in the scaffold are fused together, ensuring that the structure and the mechanical property of the microsphere-based scaffolds are suitable for applications where appropriate mechanical properties are required [39–41]. Qutachi et al. reported that scaffolds made by compressively molding PLGA microspheres at 37 °C [41] have mechanical strengths suitable for cell attachment and proliferation in tissue engineering. The porosity of the microspheres was achieved by surface treatment using ethanolic sodium hydroxide.

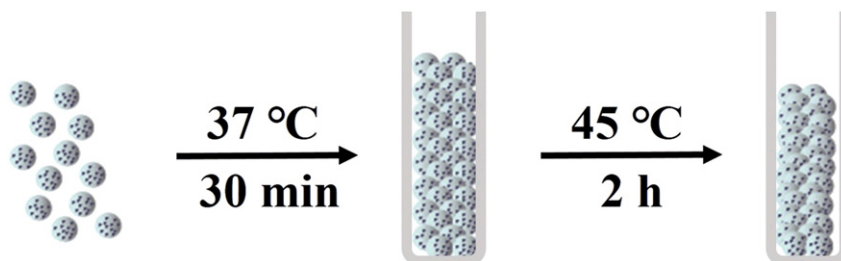


Fig. 2. A schematic illustration showing the preparation of an I-shape scaffold using porous microspheres.

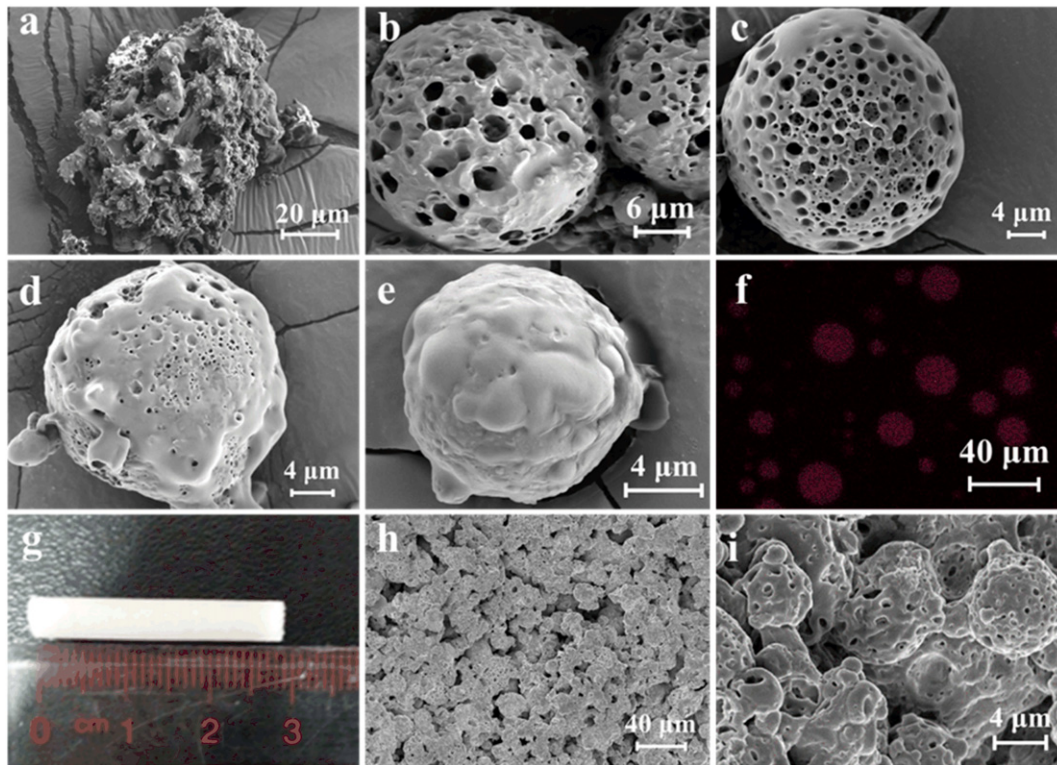


Fig. 3. SEM images of A_1 (a), A_2 (b), A_3 (c), A_4 (d), A_5 (e). The CLSM image in (f) is due to the fluorescence of rhodamine B in the PLGA microspheres containing vancomycin-rhodamine B. Shown in (g) is a photograph of an I-shape scaffold made of PLGA microspheres A_2 . The SEM images of the cross section of the PLGA scaffold in (g) at different magnifications are shown in (h) and (i).

3.2. In vitro characterization of microspheres and scaffold

Shown in Fig. 4 are the in vitro release profiles measured at 37 °C (the normal body temperature) for microspheres A_2 and a scaffold fabricated using the same kind of microspheres. The reason for using microspheres A_2 is because they have the highest vancomycin encapsulation (30%) in comparison with microspheres made under other coagulating bath conditions [24]. For both the microspheres and the scaffold, burst release [8] is observed in the first half a day, within which the cumulative drug release from the microspheres and the scaffold is 59% and 37%, respectively. We thus achieved a significantly lower burst release

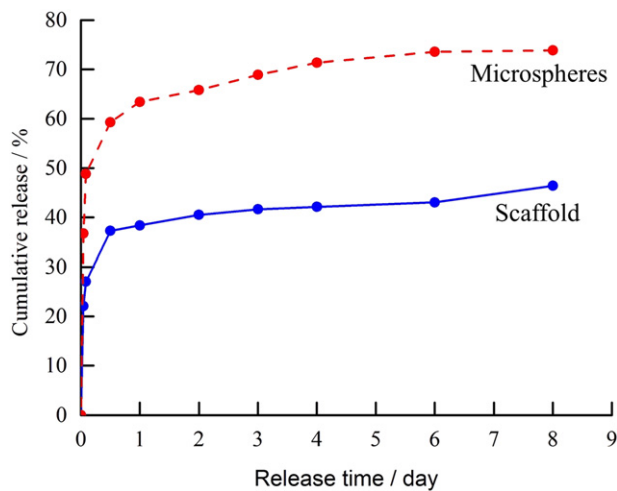


Fig. 4. In vitro drug release profiles of vancomycin-loaded porous microspheres and a scaffold made by compression molding of microspheres. The release profiles were obtained at 37 °C.

from the scaffold in comparison with the microspheres. The cumulative release from the scaffold is relatively steady during the tested period (i.e., 8 days) compared to that of the microspheres. On day 8, cumulative drug release from the microspheres and the scaffold increased to 74% and 46%, respectively. The much higher drug release rates observed in microspheres are because they have a much higher surface area to volume than a scaffold.

In our in vitro release experiment carried out in PBS, the dispersed microspheres all have their entire surface in contact with the solution. By contrast, only the outermost layer of microspheres of the scaffold in PBS is in contact with the solution. Assuming that the drug is uniformly dispersed throughout a polymer matrix [42], the drug release rate is inversely proportional to the wall thickness of the polymer. It is clear that vancomycin in the dispersed PLGA microspheres is easier to release into PBS compared to the scaffold system. Xiao and Brazel have reported in a simulation study that the drug diffusivity in a polymer matrix can be easily controlled through modification of the polymer structure [43]. Therefore, as our results demonstrated, scaffold systems can be used to reduce drug release rates. The release profile measured from the scaffold (Fig. 4) shows a burst release phase. If this hinders its applications, then a hydrophobic coating may be used to remove or control the burst release phase [4].

We also measured vancomycin release profiles in PBS from three I-shape scaffolds before and after a temperature surge from 37 °C to 45 °C. Other three I-shape scaffolds were used to measure their release profiles at 37 °C, serving as the control release profile. This experiment is designed to understand the impact of raised temperatures on drug release kinetics of the scaffold. Fig. 5 shows a control release profile at 37 °C and a release profile with temperature surges from 37 °C to 45 °C. In comparison with the control, the temperature surge release profile shows a release burst of 5–10% as measured at the first 1 h and days 1–3.

Fig. 5 shows that the release kinetics of the scaffold is sensitive to temperature. The behavior of the jumps in drug release upon

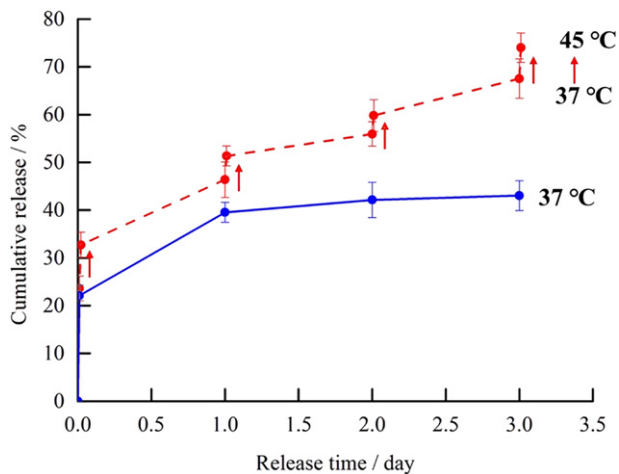


Fig. 5. Scaffold drug release profiles for the control (obtained at 37 °C) and for the temperature surge experiment carried out by increasing the temperature from 37 °C from 45 °C for 15 min.

temperature surges can be explained as follows. When the scaffold is heated to 45 °C, which is beyond its T_g , the increased movement of the polymer chains significantly enhances the overflow of the encapsulated vancomycin. On the other hand, with increased temperatures the scaffold swells, allowing water molecules in the PBS to penetrate more easily into the microspheres inside the scaffold. Such increased levels of water assist dissolving vancomycin in the microspheres, thus enhancing the diffusion of the drug agent towards the PBS solution.

3.3. Degradation of scaffold

Having shown in the above section the drug release kinetics of microspheres and a scaffold, we now investigate the degradation of the PLGA scaffold that was incubated in PBS at 37 °C for 20 days. Another scaffold with a length of 30 mm and a diameter of 2.5 mm was freeze-fractured to make a cross section so that SEM can be used to examine changes in surface morphology during the degradation test. Shown in Fig. 6a is an SEM image of the freeze-fractured cross section of the scaffold that was 10 mm long. The magnified SEM image of this initial cross section in Fig. 6b shows that the scaffold is characterized by porous microspheres, between which there are numerous voids. It is worth mentioning that the scaffold is characterized by microscale pores from the microspheres and larger-scale voids between microspheres. This multiscale porosity is advantageous for bone repair as the macroporosity enhances osteogenesis by securing paths for cell and ion transport, while the microporosity improves bone growth into the scaffold by increasing surface area for protein adsorption and providing attachment points for osteoblasts [16].

On day 10, the SEM image in Fig. 6c shows that the microspheres in the scaffold were eroded severely, losing both the porosity of and the voids between the microspheres observed on the initial surface. On the last day of the degradation test, as evidenced in Fig. 6d, the cross

section of the scaffold was significantly smoothed out, leaving no apparent structures of individual microspheres.

Beside the morphological changes associated with PLGA degradation shown in Fig. 6, we also measured weight losses and pH changes, which are shown in Fig. 7a and b, respectively. The figure shows acceleration in weight loss beyond day 10 with a significant drop in solution pH, indicating two different degradation stages. At the beginning stage of the degradation test the ester bonds in PLGA are hydrolyzed randomly [44]. In this process, the scaffold decomposes to lactic acid, glycolic acid and other lower-mass polymeric by-products via ruptures of ester bonds in PLGA. The diffusion of these materials to the PBS solution is relatively time consuming, which is thus characterized with lower rates of weight loss. The second degradation stage is defined when the rate of weight loss accelerates and the pH of the solution drops significantly, which occurs at around day 10. At this stage, the vast majority of vancomycin hydrochloride has been released from the scaffold into the PBS, pH values decrease significantly. This accompanies accelerated degradation of the scaffold [8].

In comparison with PLGA films [45], foams [46] and 3D porous scaffolds prepared via compressing pasty PLGA [47], our porous scaffold has a faster degradation rate. This is due to the fact that our scaffolds are made of porous microspheres, which provide a much higher surface to volume ratio than all of the forms of PLGA film, foam and scaffold reported by other researchers [45–47]. Therefore, our porous scaffold is suitable for applications requiring faster a completion time in the range of 2–3 weeks.

3.4. Shape-memory effect of scaffolds fabricated using vancomycin-loaded PLGA microspheres

Shown in Fig. 8 is the shape-memory effect of a scaffold fabricated using vancomycin-loaded PLGA microspheres. Fig. 8a and b show the permanent I-shape and the temporary U-shape of a scaffold, respectively. As detailed in the experimental section the U-shape scaffold was formed by bending the I-shape at 45 °C followed by cooling the scaffold to 4 °C. Fig. 8c shows the recovered I-shape scaffold when the temporary U-shape scaffold was heated to 45 °C for 27 min. The length of the permanent I-shape before and after the recovery is 29.5 and 29.0 mm, respectively, suggesting a recovery ratio of 98%. We also tested three other scaffolds, whose permanent J-, N- and U-shape and temporary shapes are shown in Fig. 8d and e, respectively. The recovery of the temporary shape to the permanent shape of each of the three scaffolds at 45 °C for 10 and 26 min is shown in Fig. 8f and g, respectively.

Therefore, our scaffolds made by compression molding of PLGA microspheres loaded with vancomycin possess shape-memory effect [26, 28], which can be explained as follows. When the microspheres are compressively molded to form a scaffold at 45 °C for 2 h, the contacting portions of adjacent microspheres are fused together. These fused spots act as the netpoints to make the permanent shape of the scaffold [26, 41]. The temporary shape of a scaffold is made via deformation of the netpoints in its initial (i.e., permanent) shape at 45 °C. The temporary shape can be kept at any temperatures lower than 45 °C once the deformation forces [26] are removed at 4 °C. When the scaffold is heated to

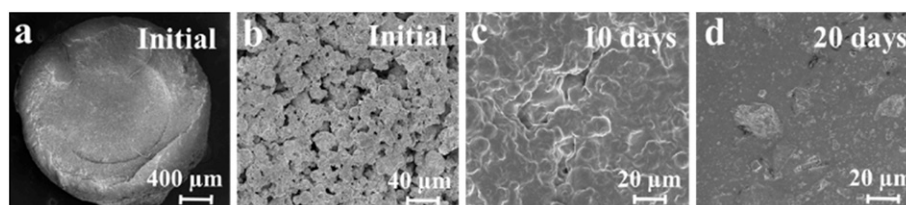


Fig. 6. SEM images of the freeze-fractured cross section of a scaffold at different magnifications (a and b) and its changes in 10 days (c) and 20 days (d). A scale bar is inserted in each image.

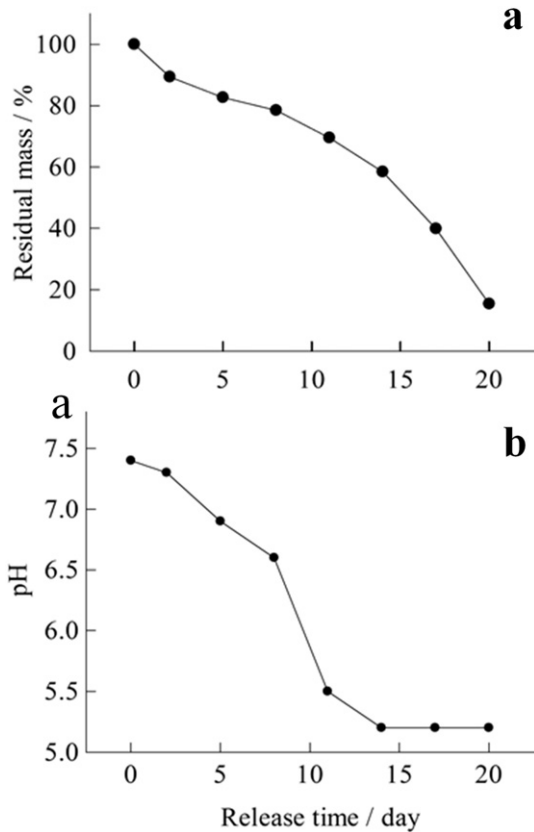


Fig. 7. Degradation of a scaffold (made by vancomycin-loaded PLGA microspheres) as examined by (a) its residual mass and (b) variation of pH values of the PBS. The PLGA scaffold was immersed in PBS maintained at 37 °C and vibrated at a frequency of 100 cycles/min.

45 °C, the deformed netpoints recover to their permanent states, realizing a recovery of the temporary shape to the permanent one.

Coupling the convenience of tailoring drug agents in PLGA microspheres with the ease of fabrication of shape-memory scaffolds using microspheres, our scaffold fabrication approach is likely to find applications in bone tissue regeneration. In this tissue engineering, it is important that (a) biomolecules assisting tissue formation and antibiotics preventing bone infection [6] are readily encapsulated to the microspheres [6] and (b) the shape-memory effect of scaffold can be used to accommodate challenging spatial limitations in the implanted environment [25].

4. Conclusions

We demonstrated that vancomycin-loaded porous PLGA microspheres (shear precipitated via Poiseuille flow generated in their emulsion in coagulating bath) can be readily compressively molded to form scaffolds, in which the adjacent microspheres are fused together. Our drug release tests conducted at the body temperature (37 °C) confirmed that the scaffolds had a much lower release rate in comparison with that of microspheres. For example, the burst release (in half a day) for microspheres and a scaffold was approximately 40% and 60% in cumulative release, respectively. With a glass transition temperature of 42 °C, the drug release from the PLGA scaffolds was found to be sensitive to temperature as evidenced by a 5%–10% jump in cumulative release when temperatures surged from 37 °C to 45 °C. The biodegradability of an I-shape scaffold (10 mm in length and 2.5 mm in diameter) was confirmed in a 20-day degradation test carried out in PBS at 37 °C. Moreover, we found that our scaffolds have shape-memory effect. Their temporary shapes recovered to their permanent ones once the scaffolds were returned to 45 °C. This will lead to applications of our scaffold system in bone regeneration where both the use of antibiotics against infection and accommodation to spatial restriction are encountered. We thus have demonstrated our scaffolds on their biodegradability,

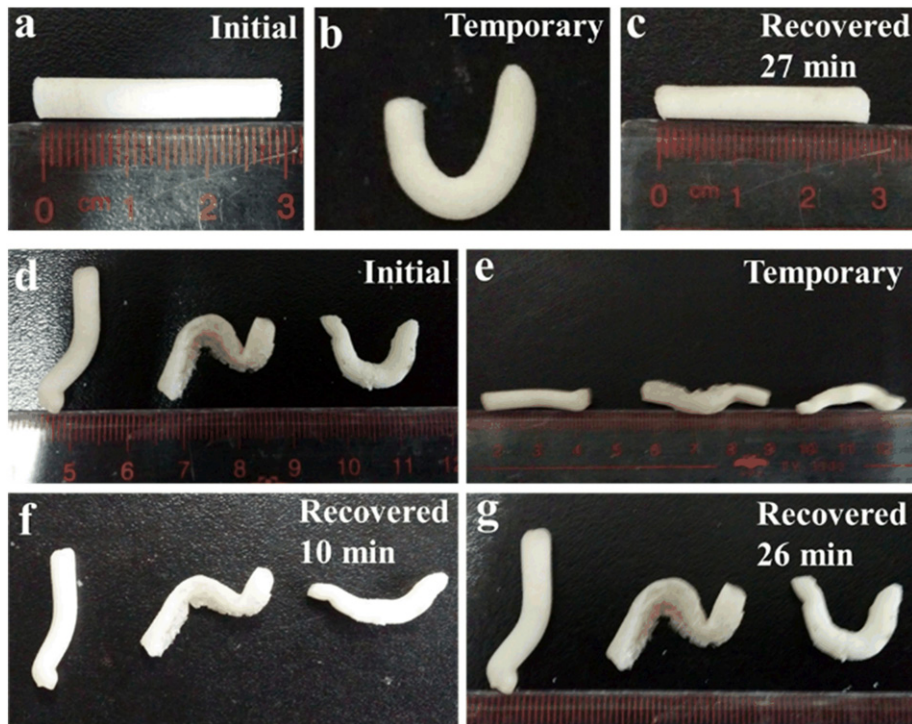


Fig. 8. Photographs of the scaffolds made of vancomycin-loaded PLGA microspheres showing their initial (i.e., permanent), temporary and recovered shapes. The permanent I-shape scaffold (a) was transformed to the temporary U-shape (b) made at 45 °C followed by being cooled down to 4 °C. Then, the temporary scaffold was recovered to I-shape by heating it to 45 °C (c). Other examples of permanent J-, N- and U-shaped SMP scaffolds (d) show their temporary shapes (e) recovering at 45 °C for 10 min (f) and 26 min (g).

shape-memory effect, processability using drug-loaded porous PLGA microspheres and controllable drug release. Our goal is to create more sophisticated structures using advanced technology such as 3D printing using our drug-loaded porous microspheres as the source.

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