Poly (ε-caprolactone) coating delays vancomycin delivery from porous chitosan/β-tricalcium phosphate composites

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Abstract: The orthopedic infection, such as osteomyelitis, especially those caused by Methicillin-resistant Staphylococcus aureus (MRSA), remains a major complication resulting in severe fractures. Local vancomycin delivery is considered to provide better methods when avascular zones prevent the delivery of drugs from conventional routes of administration. Chitosan (CS) delivery system has been developed with the disadvantages, such as mechanically weakness, lacking osteoconductivity, and the initial burst of antibiotics into the environment. The aim of this study was to confirm that the prepared CS/β-TCP composites with PCL of three different concentrations. The morphological structure of composites, including pore size and porosity, was examined. The result showed that CS/β-TCP coating delays vancomycin delivery from porous CS/β-TCP composites in a sustained and controlled manner for 6 weeks at levels to inhibit MRSA proliferation. Therefore PCL coating could be used to retard the release of vancomycin from CS/β-TCP composites coated with PCL might be one of the candidate vancomycycin carriers for treating MRSA-related osteomyelitis.

Key Words: osteomyelitis, CS/β-TCP composites, polymer coating, drug-delivery systems (DDSs), controlled release


INTRODUCTION

Despite the great improvement of the surgical techniques and modern advances in antibiotic therapy, the orthopedic infection, such as osteomyelitis, especially those infection caused by Methicillin-resistant Staphylococcus aureus (MRSA), remains a major complication resulting in severe physical, mental, and economic hardship. Till currently, the treatment of osteomyelitis primarily involves the surgical debridement of necrotic tissue, irrigation with an antibiotic solution, and the application of a systemic antibiotics administration for 6 weeks. Vancomycin is an effective antibiotic against MRSA, however, large doses of parental vancomycin cannot penetrate efficiently into local avascular zones. Furthermore, long-term systemic administration of vancomycin is associated with a high incidence of nephrotoxicity, ototoxicity, and gastrointestinal side effects, as well as an increased cost and low patient compliance. Therefore, new carrier systems for the local release of vancomycin should be explored to improve the therapeutic efficacy.

Among the local antibiotic delivery systems that have been developed to treat osteomyelitis, natural polymers, such as proteins and polysaccharides, are attractive due to their flexibility in obtaining a desirable drug release profile, cost-effectiveness, broad range of physicochemical properties, and broad regulatory acceptance. Chitosan (CS), a mucopolysaccharide, is the alkaline deacetylated product of chitin and has structural similarities to glycosaminoglycan. CS with favorable properties such as nontoxic, nonallergenic, biocompatible and biodegradable, is such a promising material that could be used in drug delivery systems (DDSs).

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CS has been processed into several forms to be used in tissue engineering applications, such as membranes, particles, fibers, and 3D fiber meshes. When made into porous structure, CS can provide a scaffold for bone cells to grow in and accelerate cell proliferation. The DDSs based on CS are able to carry active agents or biomolecules and growth factors. In addition, the preparation of these systems involving freeze-drying or lyophilizing a CS gel solution, is normally uncomplicated. However, CS-based materials for local antibiotic treatment of bone infections still have some drawbacks like mechanically weakness and lacking osteoconductivity. Current attempts are focused on improving the mechanical and biological properties of CS composites through the incorporation of bioceramics such as hydroxyapatite (HA) and β-tricalcium phosphate (β-TCP). In recent years, integrating calcium phosphate materials into DDSs for local antibiotic treatment of bone infections has been extensively studied. By integration calcium phosphates into CS, the reinforcement on the mechanical behavior and the improvement of osteoconductivity of CS scaffolds could be achieved.

CS is pH sensitive, which makes it difficult to control the drug-release behavior under various pH values of the internal human organs. Another disadvantage of CS-based carrier is the initial burst of antibiotics into the environment, like the other biodegradable polymers. Coating with another degradable hydrophobic polymers is one of the methods to delay the delivery of the water-soluble drugs. Polycaprolactone (PCL) is such a kind of biodegradable aliphatic polymer with good biocompatibility and hydrophobicity. PCL is also an ideal material for its valuable properties such as nontoxicity for organism and gradual resorption after implantation. We reasoned that the CS/β-TCP composites combined with vancomycin coated with PCL could hinder the initial burst effectively and provide longer antibiotic delivery.

In this study, we fabricated porous CS/β-TCP composites as vancomycin delivery carriers and coated them with PCL. The microstructures and the physical characterizations were measured and compared. The vancomycin release profiles were observed in vitro. The aim of this study was to confirm that the prepared CS/β-TCP composites coated with different concentrations of PCL, similar to natural bone in components, had a three-dimensional porous structure and could be used as drug carriers to deliver vancomycin in a sustained and controlled manner effectively for 6 weeks at levels to inhibit MRSA proliferation.

MATERIALS AND METHOD

Materials
CS (M_w = 200,000 Da, deacetylation degree is 91%) was purchased from Marinard Biotech Entrepot, Canada. The β-TCP powder was provided by Ensail Beijing, Beijing, China. Vancomycin was purchased from Eli Lilly, Suzhou, China, and PCL (M_w = 80,000 Da) was purchased from BrightChina Industrial, Shenzhen, China. Phosphate buffered saline (PBS, 0.01M phosphate buffer, 0.0027M potassium chloride, and 0.137M sodium chloride, pH 7.4) was prepared in our lab. All other reagents, such as acetic acid, ethanol, dichloromethane, and sodium hydroxide, were analytical grade, purchased from Sinopharm Chemical Reagents, Shanghai, China, unless stated otherwise.

Methods
We designed an in vitro study to assess the weight increment, microstructure (pore size and porosity), water uptake, thermogravimetric analysis, and in vitro drug release profile of three composite types: vancomycin-containing CS/β-TCP composites coated with (1) 1.25w/v%, (2) 2.5w/v%, and (3) 5.0w/v% PCL, and the vancomycin-containing CS/β-TCP composites without coating served as a control group. The ratio of CS, β-TCP, and vancomycin was set as 1:1:1.

Preparation of CS/β-TCP composites
CS dissolved in 1.0v/v% acetic acid was prepared beforehand and the pH was 4.21. The mixture was stirred at 25°C for 2 h to obtain a homogeneous polymer solution and centrifuged under 12,000 rpm to remove the undissolved particles. Vancomycin (200 mg) powder was dissolved in 1 mL PBS and mixed with 10 mL CS solution (containing 200 mg CS) in a 25-ml sterile beaker, followed by magnetic stirring for 60 min.

After milling for 8 h, the mean particle size of β-TCP powder was 10.6 μm (measured by laser particle analyzer). β-TCP powder (200 mg) was first ultrasonically dispersed in 1 mL of deionized water for 2 h. Subsequently the dispersed particles were added drop by drop to the CS/vancomycin solution while being agitated. The CS/β-TCP/vancomycin dispersion was vigorous mixed using a magnetic stirrer for 1.5–2 h to obtain a homogeneous mixture.

Samples were fabricated by freezing and lyophilization of CS/β-TCP/vancomycin mixture. The obtained CS/β-TCP/vancomycin dispersion was transferred to polystyrene cylindrical molds, and frozen at −20°C for 48 h. Then the frozen samples were moved into a freeze-dryer (LGS-4, Xing Zong Vacuum Technology, Shanghai, China) at a preset temperature of −5°C, and freeze-dried at 0.5 mmHg for 4 days to completely remove the solvent. After lyophilization, the samples were neutralized in 10w/v% sodium hydroxide solution to remove the residue of acetate molecules, that are in solid form as ions bound to the cationic amine groups in the CS, to avoid the scaffold from swelling rapidly and dissolved ultimately upon rehydration in a neutral aqueous medium. Thereafter, samples were rinsed with deionized water until a neutral pH was achieved. The hydrated samples were refrozen for a period of an hour at −80°C. The frozen samples were relyophilized for 48 h. All the rinse water was collected separately to determine the vancomycin loss (V), the amount of vancomycin that was washed out during the rinse process.

Coating of the composites with PCL
Twenty milliliters of PCL dissolved in dichloromethane with three different concentrations (1.25w/v%, 2.5w/v%, and 5.0w/v%) were prepared beforehand. The CS/β-TCP/vancomycin cylinders were sliced into thin disks (2 cm² area, 1804 FANG ET AL. POLY (L-CAPROLACTONE) COATINGS DELAYS THE DELIVERY OF VANCOMYCIN
3.0 mm thickness), and then were dipped into the three different PCL solutions mentioned above for 5 min. During this time, they were put under a controlled vacuum of 22 mmHg for 20 s to drive PCL solution to infiltrate into the pore structure. The disks were subsequently transferred into a self-designed cage, which was connected on the Laboratory Mixer (HENC, Shanghai, China), 600 rpm for 40 s, to remove the extra polymer solution (Figure 1). All the samples were dried for 72 h under vacuum at room temperature.

Four groups of the samples were prepared: Vancomycin-containing CS/β-TCP coated with (1) 1.25w/v% PCL, (2) 2.5%w/v PCL, (3) 5.0w/v% PCL, and (4) Vancomycin-containing CS/β-TCP without coating.

**Weight increment measurement**

Each disk was weighed on a precision weighing balance (CPA1003P, Sartorius Mechatronics, Beijing, China) before and after the coating process. After accurate weighing, the weight increments of the samples were recorded. We randomly chose out 10 pieces from each group to get the average. The experimental data are expressed as Means ± SD.

**Microstructure of composites**

**Scanning electron microscope.** The structural morphology of composites was examined by scanning electron microscope (SEM) (TeScan5136MM, 20 kV). The samples were mounted on aluminum stubs with conductive paint and were sputter-coated with gold (10 mA−120 s).

**Pore size.** Pore diameter was estimated from SEM micrograph. The pore size was estimated using a minimum of 30 pores from different places of the cross-section of the scaffolds. Three scaffolds of each group and three different cross-sections of each scaffold were used to estimate pore size (Mean ± SD).

**Porosity values.** The porosities of the composites were determined using a liquid displacement method. Specifically, each specimen was immersed in a graduated cylinder containing a known volume ($V_1$) of ethanol. The cylinder was placed in vacuum to drive ethanol to infiltrate into the pore structure of the scaffold. The total volume of the remaining ethanol and the ethanol-infiltrated scaffold were then recorded as $V_2$ by reading the level of the graduated cylinder. The ethanol-infiltrated scaffold was then removed from the graduated cylinder and the residual volume of ethanol was recorded as $V_3$. On the basis of these data, the bulk volume ($V_b$) of the scaffold can be calculated as $V_b = (V_2-V_1)+(V_1-V_3)$, and finally, the porosity ($P$) of the scaffold as $P = (V_1-V_3)/(V_2-V_3)$. Six repeated measurements...
were conducted for each sample to calculate the average value and corresponding standard deviation.

**Water uptake test**

The water uptake of the three PCL coated and uncoated CS/β-TCP (n = 6/group) were measured as follows. At first, the composites were cut into cuboid 1 cm x 1 cm x 0.5 cm and their dry weights were measured. Then, they were immersed in PBS and equilibrated at room temperature for 1 hr. Then the wet samples were removed from the PBS, blotted with filter paper to remove any excess solution, and weighed. Water uptake was calculated as dividing the amount of PBS absorbed by the dry weight of each sample.

**Thermogravimetric analysis**

TGA was conducted with a Perkin Elmer/Pysis1 Thermal Analyzer (Perkin-Elmer Corp. Norwalk, VA) in air atmosphere at a flow rate of 80 mL/min. Samples of 2 mg were heated from 50°C to 800°C at a rate of 10°C/min.

**In vitro drug release studies**

In order to analyze the vancomycin release behavior, the specimens were immersed in polyethylene vials with 10 mL of PBS. The vials were sealed tightly and incubated at 37°C without stirring. Half of the medium was withdrawn at predetermined periods of time (24, 48, and 72 h, then every 24 h till 14 days, and then every 3 days till 42 days) and replaced with an equivalent amount of fresh PBS. The concentration of vancomycin was determined by measuring the absorbance at 280 nm using a UV spectrophotometer in a UV-Vis (Shimazu UV 2201). Each absorbance value was converted to the drug concentration using a standard curve, which was drawn by measuring the optical absorbance of the vancomycin dissolved in the PBS with concentrations in the range of 4–500 µg/mL. A linear relationship between the vancomycin concentration (x) and the optical absorbance (y) was obtained (y = -8.47375E-4 + 0.00405x).

The actual mass of drug released was calculated based on the measured concentration and actual withdrawn sample volumes. The cumulative percentage release was calculated as the ratio of the mass released at each time point to the amount of vancomycin (Vc) embedded in the composites. The Vc was calculated by using the formula as Vc = Vt − Vr. The cumulative release data were fitted to a logarithmic function, which was differentiated with respect to time in order to calculate the daily percentage release. All experiments were repeated three times, and the experimental data are expressed as Means ± SD.

**Data analysis**

In all the experiments a minimum of six samples were used. Obtained values in each experiment were normalized with the control samples. Results are expressed as the means of at least five replicates ±SD. Statistical analysis was performed using the one-way analysis of variance (ANOVA) with 95% confidence interval.

**RESULTS**

**Microstructure of the composites**

The visual examination of all newly lyophilized CS/β-TCP and vancomycin composites showed that they were white, stiff, and inelastic, while the hydrated neutralized composites were a bit more flexible and elastic.

On the basis of the quantitative analysis of a number of micrographs, the pore size was 145 ± 35.4 µm (range 50–175 µm). β-TCP did not alter the microstructure of the composites. The cross-sectional view of the composites indicated uniform pore structure from top to bottom [Figure 2(A,B)] and the high magnification SEM micrograph suggests the interconnected pore structure [Figure 2(C)] with uniform and nonagglomerated distribution of β-TCP particles within the CS matrices, including the pore wall [Figure 2(D)]. The porosity of the composites was more than 90% (Range 92.0–95.5%).

Representative microstructures of CS/β-TCP composites illustrating highly porous structure on the top surface and cross section plane are presented in Figure 3(AB). It is believed that the electrically charged nature of CS network is helpful in the uniform distribution of β-TCP. After coating process, a PCL coating layer was formed on the surface of CS/β-TCP. For the composites coated with 1.25w/v% PCL, there’s barely noticeable polymer on the surface of the material, and most of the area was not sealed [Figure 3(A)]. Only some silk-drawing-like polyester could be observed [Figure 3(B)]. After coated with 2.5w/v% PCL, photomicrographs obtained by SEM showed a thin coating layer existed on the surface of the composites, with small amount of unsealed area [Figure 3(C,D)]. In the composites coated with 5.0w/v% PCL, most of the pores on the surface were filled by thick polyester [Figure 3(E,F)] Therefore, among the three coated groups, 2.5w/v% PCL coating group has the most morphologically ideal coating layer on the surface of CS/β-TCP composites.

**Weight-increment after coating**

Weight-increment after coating process can be considered as the total amount of the PCL that has been coated on the material. As is shown in Table I, after being coated with 2.5w/v% PCL solution, CS/β-TCP could get the best weight gain ratio of 52.49 ± 23.19%, while the weight gain of the other two groups were significantly lower [Figure 3(G)].

**Thermogravimetric analysis**

TGA curve of CS/β-TCP composites with or without PCL coating was shown in Figure 4. In the TGA analysis, the maximum decomposition temperature for CS was 313°C, and that of PCL is around 388°C [Figure 4(A)]. The TGA of the CS/β-TCP with or without PCL coating showed a monotonic weight loss at the temperature interval of 300–350°C due to the decomposition of CS, and thereafter, a sharp decomposition step with complete weight loss at 400°C due to the decomposition of PCL [Figure 4(B)]. The TGA result showed that the thermal stability of CS was slightly reduced upon physically mixing it with β-TCP and vancomycin.
Water uptake
The weight of coated and uncoated groups increased after being saturated in aqueous solution in comparison with the dry material. The total wet weight of the material, which indicated water uptake ability of the coated CS/β-TCP was significantly lower than the uncoated composites. The ratios of wet weight to dry weight of the samples were: 4.90 ± 0.24 for 1.25w/v% PCL-coated group, 4.60 ± 0.11 for 2.5w/v% PCL-coated group, 2.30 ± 0.12 for 5.0w/v% PCL-coated, and 5.80 ± 0.21 for uncoated control group (Figure 5). The difference between each group was statistically significant. The result of water uptake test showed that the water uptake was significant reduced with the elevation of the concentration of the PCL.

In vitro drug release
We observed the in vitro drug release from the uncoated CS/β-TCP composites and the other three groups coated with the PCL. Three mathematical models including zero-order, first-order, and the Higuchi model were employed to characterize the release behavior of vancomycin.

Uncoated CS/β-TCP. As depicted in Figure 6, there was a huge peak of drug release on 1 day, and the cumulative drug release percentage was 32.3 ± 2.4%. The most commonly used model for a mathematical description of drug delivery kinetics is the Peppas model [Eq. (1)], where the cumulative release $M$ (%) is proportional to a release constant $k$ (h$^{-1}$) and follows a time to the power of $n$ relation with $n$ being the release exponent:

$$M = k \times t^n \quad (1)$$

Here, $k$ is indicating the release rate, whereas $n$ allows a characterization of the release mechanism. It is also in good agreement with the release kinetic of vancomycin from CS/β-TCP matrices in this study since the assumptions of this model like a homogeneous drug loading, a fast drug dissolution compared with drug diffusion and drug release due to a concentration gradient are fulfilled. According to the values of $n$ (0.52), the drug release of the uncoated sample can be considered as controlled by Fickian diffusion.

Composites coated with 1.25w/v% PCL. The cumulative drug release of 1 day was 8.12 ± 0.5%. The initial burst happened on 3 days, and the cumulative drug release percentage was up to 40.24 ± 0.8%.

Composites coated with 2.5w/v% PCL. A three-phase profile of degradable drug delivery curve was obtained, as the other researches. The drug release of 1 day was 7.12 ± 2.3%, zero-order model can fit the release profile more than the other two models during 0–14 days, the initial drug

FIGURE 2. SEM of the CS/β-TCP/vancomycin composites before coating. A: The microstructure on the top surface; B: The microstructure of the cross section plane; C: Pores with smaller size range 40–50 μm could be found on the pore wall, indicating that the pores are interconnected with these small pores; D: The β-TCP particles distributed homogenously on the surface and the pore wall of the composites.
might release from the unsealed area, while after 14 days, there was a plateau phase in which polymeric encapsulation retarded diffusion of vancomycin (14–30 days) followed by a quantitative release within 30–42 days.

**Composites coated with 5w/v% PCL.** The drug release of 1 day was 5.12 ± 2.4%. The burst release appeared on 7 days, the cumulative percentage release rose steeply from 17.88 ± 3.2% (6 days) to 30.35 ± 2.1% (7 days).

**DISCUSSION**

Infection of bone and joint is a significant threat to patient health. To eradicate infection, it is essential to maintain antibiotics at the therapeutic concentration at the implantation site for an extended period of time. An ideal local drug carrier to treat osteomyelitis should be bioactive, porous to ensure the materials to bond to the bone tissue. The carrier should be resorbable as well, to allow its progressive substitution by newly formed bone, and to avoid the second surgery to remove the carriers. CS has some interesting characteristics, such as the ability to be molded in various geometries and forms such as porous structures, suitableness for cell ingrowth, and osteoconductivity. In recent years, considerable attention has been given to CS-based materials and their applications in the field of orthopedic tissue engineering. Because of its favorable gelling properties CS can deliver morphogenetic factors and pharmaceutical agents in a controlled fashion. The CS/β-TCP composites could be used as DDSs for antibiotic to treat osteomyelitis. One disadvantage of biodegradable CS used for controlled release is the initial burst of antibiotics into the environment and an advantage of β-TCP is its osteoconductivity. Given the hydrophobicity of PCL, we reasoned that the CS/β-TCP composites combined with vancomycin coated with PCL could hinder the initial burst effectively and provide longer antibiotic

<table>
<thead>
<tr>
<th>The Concentration of PCL (%)</th>
<th>1.25</th>
<th>2.5</th>
<th>5.0</th>
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<tbody>
<tr>
<td>Weight before coating (mg)</td>
<td>28.37 ± 3.18</td>
<td>28.86 ± 3.05</td>
<td>27.47 ± 1.44</td>
</tr>
<tr>
<td>Weight after coating (mg)</td>
<td>39.30 ± 3.07</td>
<td>43.45 ± 3.08</td>
<td>37.40 ± 2.87</td>
</tr>
<tr>
<td>Weight increment ratio (%)</td>
<td>39.16 ± 8.48</td>
<td>52.49 ± 23.19</td>
<td>36.22 ± 9.56</td>
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delivery. We therefore developed a vancomycin-containing CS/β-TCP composites coated with PCL, characterized it according to its pore structure, pore size, porosity, and assessed its vancomycin release profile. The TGA result of this study indicated that the vancomycin, CS, and β-TCP in the composites interacted with each other. But there was no new chemical compound formed in the composites. That means there was no chemical reaction happening during the preparation of the composites. Vancomycin and β-TCP were still in their original state after integrated into the composites.

HA and β-TCP, are excellent candidates for bone repair and regeneration because their chemical compositions are similar to that of the mineral phase of natural bone, and they have been shown to be osteoconductive. β-TCP was selected as our model calcium phosphates, because β-TCP is more resorbable than hydroxyapatite in a biological environment. The degradation rate of β-TCP is 10 times higher than that of HA. When the CS/β-TCP composites was immersed in PBS, the pH value of the solution was controlled by the dissolution of calcium phosphate, and acidic degradation byproducts from CS were buffered. The improvement of osteoconductivity could be achieved through the incorporation of calcium phosphates into the CS matrix.

There are some limitations of our study. First, this is an in vitro study with limited conditions and times of assessment; further in vivo and clinical studies would be required to confirm the validity of the approach. Second, bacteriostatic or bactericidal activity of the withdrawn liquid at the different time points during the drug release study were not tested, although the final vancomycin concentration was still higher than MIC of MRSA. That may lead the concern about the effectiveness of the delivered vancomycin. Third, as the protocol, we only tested three different concentrations of PCL as coating solution, maybe other concentrations of PCL would work better than the 2.5w/v%, that may needs further investigation. Fourth, this is only a preliminary research without testing the cytotoxicity and biocompatibility. The cell adhesion, proliferation, and mineralization were not assessed.

In the uncoated group, it showed that the release rate of initial phase is faster than that of terminal phase. Due to the slow degradation rate of CS/β-TCP in PBS solution, the diffusion and dissolution of vancomycin might contribute to the rapid release at the initial phase. After being coated with 2.5w/v% PCL, the weight of the CS/β-TCP was increased by 52.49 ± 23.19%, which is the highest among the three groups. The viscosity of 1.25w/v% PCL was relatively lower, therefore most of the PCL solution could not stay in the material during the spinning process. On the other hand, the 5.0w/v% PCL was too viscous to get into the pore structure during the vacuum process and then most of the PCL solution remained above the surface and would be easily removed during the spinning process.
ensures that a steady amount of drug is released over time, minimizing potential peak/trough fluctuations and side effects, while maximizing the amount of time the drug concentrations remain within the therapeutic window. The release profile of vancomycin from 2.5w/v% PCL coated group followed a near zero-order release within 14 days, and the quantitative release extended to 42 days. Empirically, that might be an enough long period of time for antibiotics release to treat the osteomyelitis caused by MRSA²¹, although there are no clinical studies or documented records indicating the superiority of the 4-6-week course of antibiotics over other durations.²⁶

CONCLUSIONS
To conclude, PCL coating could be used to retard the release of vancomycin from CS/β-TCP composites in a sustained and controlled manner. Porous CS/β-TCP coated with PCL might be one of the candidate vancomycin carriers for treating MRSA related osteomyelitis.

REFERENCES

FIGURE 6. In vitro release profile of vancomycin from the CS/β-TCP composites coated/uncoated with different concentrations of PCL, in PBS (pH 7.4) at 37°C.

2.5w/v% PCL was proved to be able to work as a coating solution to form morphologically ideal coating layers among the three coated groups.

The water uptake was significant reduced with the elevation of the concentration of PCL resolution. The difference between each group was statistically significant. The reason might be that the coated hydrophobic PCL could hinder water from intrusion into the material to contact with hydrophilic CS directly after the material was immersed in PBS. As to the 5.0w/v% PCL coated material, polyester sealed most of the surface, so that PBS is hard to enter the inner part, thus its ability of water uptake reduced significantly. The hydrophobic coating hindered the diffusion of the hydrophilic vancomycin at the early stage. Since the viscosity of 5.0w/v% PCL is relatively high, most of the pores walls and the inner part of the materials were not coated, after the outer layer of the PCL was lifted by the intruded PBS, the water soluble drug embedded in the composites then burst out on 7 days.

Traditionally, osteomyelitis has been treated with parenteral antibiotics for with 4–6 weeks after definitive debridement surgery. Antibiotic-impregnated beads have also been used as adjuvant therapy for chronic osteomyelitis.²⁵ Zero-order mechanism ensures that a steady amount of drug is released over time, minimizing potential peak/trough fluctuations and side effects, while maximizing the amount of time the drug concentrations remain within the therapeutic window. The release profile of vancomycin from 2.5w/v% PCL coated material followed a near zero-order release within 14 days, and the quantitative release extended to 42 days. Empirically, that might be an enough long period of time for antibiotics release to treat the osteomyelitis caused by MRSA²¹, although there are no clinical studies or documented records indicating the superiority of the 4-6-week course of antibiotics over other durations.²⁶