Ofloxacin-Delivery System of a Polyanhydride and Polylactide Blend Used in the Treatment of Bone Infection

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Received 23 August 2006; revised 26 January 2007; accepted 9 February 2007
Published online 4 April 2007 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jbm.b.30832

Abstract: We developed a local drug-release system consisting of two biodegradable polymers, poly(sebacic anhydride) (PSA) and poly-D,L-lactide (PLA), for the treatment of chronic osteomyelitis. PSA and PLA were dissolved and blended at different ratios in tetrahydrofuran. Ofloxacin was loaded with an 8:1 weight ratio of the blend to the drug. The ofloxacin-containing beads of the PSA/PLA blend were made by preheating and compressing them in a mold. The *in vitro* drug release showed that changing the ratio between the two polymers caused the effective ofloxacin-release duration to vary from 6 to 68 days. The ofloxacin-containing beads with 10% PSA and 90% PLA produced an inhibition zone for the bacteria *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa* within 89 days of the experiment. The *in vivo* drug release of the beads in rabbits demonstrated that the average ofloxacin concentration in the local bone was 20.1 ± 10.3 μg/g, while that in the plasma was 35.6 ± 18.8 ng/mL, within 8 weeks. Roentgenography, bacterial cultures, and histological examinations showed that the local release of ofloxacin by the beads could cure osteomyelitis in rabbits. Our findings suggested that using PSA/PLA blends with different ratios as carriers for antibiotics might be useful in the treatment of chronic osteomyelitis and in the prophylaxis of bone infection. © 2007 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater 83B: 589–595, 2007

Keywords: polyanhydride; polylactide; ofloxacin; controlled release; osteomyelitis

INTRODUCTION

Acute hematogenous osteomyelitis and open-fracture infection can develop into a chronic form if the treatment measures are inadequate or ineffective. In chronic osteomyelitis, the systemic administration of antibiotics usually cannot achieve an effective level at the site of bone infection, owing to bone devascularization, sequestra formation, and so on. Furthermore, the long-term use of intravenous antibiotics can increase their toxicity and side effects. Thus, the problems associated with treating chronic osteomyelitis by the systemic administration of antibiotics represent a difficult issue for doctors. In 1978, Wahlig et al.[1] reported the release of gentamycin from PMMA beads. Later, Klemm[2] was the first to successfully use PMMA-gentamycin beads as a local antibiotic-delivery system to treat bone infection. This initiated a new and effective method for the antibiotic treatment of osteomyelitis. Subsequent research and applications of local delivery systems for antibiotics with the aim of treating osteomyelitis have made great progress. Although PMMA beads containing gentamycin have been locally used to treat osteomyelitis for decades, the drawbacks are obvious; for example, an additional surgical procedure is needed to remove the beads after the completion of drug delivery. To solve this problem, researchers have investigated and exploited a series of biodegradable materials as potential antibiotic carriers for local drug delivery.[3,4] Among these materials, poly-D,L-lactide (PLA) has been studied in the most detail and utilized most successfully.[3] In recent years, a new type of biodegradable polymer, the polyanhydride, has gradually come to the forefront. Polyanhydrides have good biocompatibility and possess the beneficial characteristic of surface erosion with uniform degradation.[5,6] Research on polyanhydrides has become a new "hotspot" in the area of controlled drug release.[4,5,7,8] Matrices carrying antibiotics and other compounds are required to provide various local drug-release durations for

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Contract grant sponsor: Natural Science Foundation of Hubei Province, Department of Science and Technology of Wuhan City, China

different medical purposes. The duration of drug release with PLA is related to its molecular weight and viscosity. Usually, lactide is polymerized with glycolic acid in various ratios to produce a copolymer, polylactide/polyglycolide, to regulate the drug-release duration.[3,9] Polyanhydrides can also be copolymerized with hydrophilic and hydrophobic monomers at various ratios to achieve different drug-release durations.[9,10] However, the synthesis of the copolymers requires complex chemical reactions, strict experimental conditions, and sophisticated fabrication technology. For these reasons, our novel experimental design involves blending a polyanhydride that can degrade rapidly together with a higher molecular weight PLA as a drug-release carrier, and adjusting the ratio between the two elements to easily regulate the duration of the overall degradation and the drug release. The properties and characteristics of the drug release by the blended polymers in this approach need to be investigated. In the current study, PLA and poly(sebacic anhydride) (PSA), which is a polyanhydride, were blended as a releasing carrier for the broad spectrum antibiotic ofloxacin. We hoped that by blending these compounds, the drug-releasing advantages of the two polymers could be combined, and that by changing the ratio of the two polymers in the blend, the drug-release duration could be adjusted to meet the needs of treatment and prophylaxis for bone infection.

MATERIALS AND METHODS

PSA (molecular weight = 3500) was obtained from Wuhan University of Technology. PLA (molecular weight = 110,000) was provided by Biomedical Material (part of Chengdu Dikang). Ofloxacin was purchased from the Pharmaceutical Department of Renmin Hospital, Wuhan University. *Staphylococcus aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922), and *Pseudomonas aeruginosa* (ATCC 27853) were provided by the Clinical Laboratory of Zhong Nan Hospital, Wuhan University.

Preparation of Ofloxacin-Loaded PSA/PLA Blended Beads

The PSA/PLA beads were made at 100:0, 80:20, 60:40, 40:60, 20:80, 10:90, and 0:100 weight ratios, with an 8:1 weight ratio between the polymeric blend and ofloxacin. PLA was initially weighed and dissolved in tetrahydrofuran. PSA and ofloxacin powders with corresponding weights were then added into the solution, and were ground thoroughly and evenly. After complete volatilization of the tetrahydrofuran, 120 mg blend was weighed, put into a cylindrical metal mold (6 mm in diameter) and preheated at 90°C for 10 min. Afterwards, the blend was compression molded at 104 MPa for 2 min and allowed to cool to room temperature. After mold stripping, all of the beads were sealed within plastic bags and sterilized with ^{60}Co at a delivered dose of 25 kGy.

In Vitro Release of Ofloxacin From the Beads

Three beads at each of the PSA to PLA ratios (100:0, 80:20, 60:40, 40:60, 20:80, 10:90, and 0:100) were placed in a vial containing 10 mL phosphate buffer (pH 7.4, 0.1*M*) in a thermostatic water bath at 37°C. The release medium was sampled at various time intervals over 96 days: 2, 5, and 10 h after the beginning of the test; every 24 h from days 1 to 14; every 2 days from days 15 to 28; every 3 days from days 29 to 58; and every week thereafter. At each sampling time, the release medium in the vials was replaced with fresh buffer to maintain the sink conditions. The collected samples were frozen at −20°C for the analysis. After the completion of the test, the ofloxacin concentration in the buffer samples was analyzed by a spectrophotometric assay in a Hitachi F-4500 spectrofluorometer at λ_{ex} 293 nm and λ_{em} 498 nm.

In Vitro Bacteriostasis Experiment

Based on the results of the *in vitro* drug release, the beads with the best ratio were chosen for bacteriostasis. In total, nine of the ofloxacin-loaded PSA/PLA blended beads were divided into three groups with three beads per group. Each bead was placed in the middle of an agarose culture medium that was separately inoculated with *S. aureus*, *E. coli,* or *P. aeruginosa*. After being incubated at 37°C for 24 h, the culture media were examined, and the diameters of the inhibition zones of bacteria around the beads were measured. Subsequently, the beads were transferred onto new culture media inoculated with the corresponding bacteria. Subsequently, the diameters of the inhibition zones were measured, and the media were replaced every 3 days until 2 months after the test. Then, the diameters of the inhibition zones were measured, and the media were replaced every week until 3 months after the test. The PSA/PLA beads without ofloxacin were placed onto culture media inoculated with the aforementioned bacteria as controls.

In Vivo Drug Release

In total, 18 rabbits, weighing 1.8–2.5 kg, were anaesthetized by intravenous injection of 30 mg/kg 3% pentobarbital. The right hindlimb was shaved, and then prepared and draped in standard sterile fashion. A longitudinal incision was made on the medial skin of the leg and the tibia was exposed. An 8 × 4 mm bone defect was then created down to the medullary cavity at the medial side of the proximal tibia. One ofloxacin-loaded bead with the best ratio between PSA and PLA was implanted into the defect. Blood samples (1.0 mL) were drawn from the vein in the ear of two rabbits 3 days after surgery and weekly thereafter until the eighth week. Subsequently, the two rabbits were euthanatized by lethal intravenous injection of pentobarbital, and a 2-cm sample of the proximal tibia centered on the defect was taken as a bone specimen using aseptic technique. The attached soft tissue and articular cartilage

TABLE I. Burst Release and Duration of Effective Ofloxacin Release (n = 3)

Group	Burst Release on the First Day (μg)	Percentage of Drug Release on the First Day (%)	Duration of Effective Drug Release (day)	Cumulative Release Within Duration of Effective Release (%)
100% PLA	454 ± 106*	3.4	68	55.9
10% PSA + 90% PLA	907 ± 144	6.8	49	59.8
20% PSA + 80% PLA	4279 ± 191	32.1	18	85.8
40% PSA + 60% PLA	5212 ± 185	39.1	12	87.4
60% PSA + 40% PLA	5528 ± 282	41.5	12	90.3
80% PSA + 20% PLA	5887 ± 445	44.2	12	96.3
100% PSA	5507 ± 142	41.3	6	100

* A second burst release happened in the 100% PLA group on day 33, and was comparable to the first burst.

were detached from each specimen, and the remnant of the bead was observed and removed. Subsequently, the medullary cavity was irrigated with 2 mL saline. The blood samples were centrifuged, and the plasma was taken and stored at −20°C until it was assayed for ofloxacin. The bone specimens were wrapped in tinfoil and stored in a −80°C freezer. Before analysis, the bone specimens were freeze-dried, ground into small pieces and weighed separately. Each specimen was then treated with 25% glacial acetic acid proportionally, and was soaked in it for 24 h. After centrifugation, the supernatant was removed for analysis. The plasma from the blood samples and the supernatant from the bone specimens were analyzed for their ofloxacin concentration using a spectrophotometric assay.

The ofloxacin concentrations in the plasma and the bone supernatant were determined as described previously,[11] with certain minor modifications, using a spectrofluorometer (Hitachi, F-4500). Briefly, a 0.1-mL sample was mixed with 0.01 mL saline and 0.19 mL 10% trichloroacetic acid, and then centrifuged at 1000g for 10 min. A 0.2-mL sample of the supernatant was added to 1.8 mL 0.1M acetic acid-sodium acetate buffer (pH 4.0). The solution was thermostated at 25°C and the fluorescence intensity was measured at 498 nm using an excitation wavelength of 293 nm against a blank solution. The ofloxacin concentration was quantified based on a calibration graph prepared under identical conditions.

In Vivo Treatment Against Bone Infection

Osteomyelitis Model. Using aseptic technique, an 8 × 4 mm bone defect was created on the medial side of the proximal right tibia in 20 rabbits (weighing 1.8–2.3 kg) in the abovementioned manner. A 60-μL suspension of *S. aureus* at a concentration of 1×10^8 CFU per milliliter was inoculated into each defect, and a segment of No. 7 silk thread (4 cm in length) was placed in the defect to act as a foreign body. At 4 weeks after surgery, gross observations, X-ray examinations, and bacterial cultures were used to assess whether the model of osteomyelitis had been successful.

Efficacy in Osteomyelitis. The osteomyelitis model rabbits were divided into two groups. In 12 of the rabbits, debridement was performed at the site of osteomyelitis, the thread was removed and one ofloxacin-loaded bead was placed in the bone defect of each animal. The other eight rabbits acted as a control, in which one bead without ofloxacin was implanted into each defect after removal of the thread and debridement. At 6 weeks postoperatively, gross observations and X-ray examinations were performed. The animals were then sacrificed, and tissue from the focus site of osteomyelitis was taken for bacterial culture using aseptic technique. The proximal tibia was removed aseptically, fixed in 10% buffered formalin, decalcified, and processed into paraffin. Paraffin blocks were sectioned and stained with hematoxylin and eosin (HE), while some of the sectioned slices were treated with the crystal violet-phloxine Gram stain.

RESULTS

Preparation of Ofloxacin-Loaded PSA/PLA Blended Beads

Under the heating and compression conditions, the PLA/PSA blend and the ofloxacin in the mold adhered tightly to each other. The beads were 6 mm in diameter and 3.4 mm in thickness, with a smooth surface. The beads were homogeneous, hard in nature and yellowish in appearance.

In Vitro Drug Release

Changes of Appearance and Shape. The ofloxacin-loaded PLA beads and the blended beads containing 10% PSA gradually swelled over the course of the drug-release

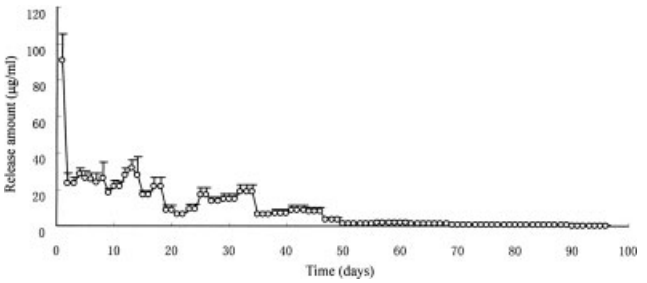

Figure 1. Daily ofloxacin release from beads containing 10% PSA (n = 3).

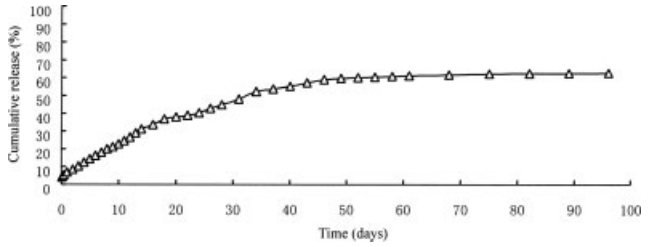

Figure 2. Percentage of cumulative ofloxacin release from beads containing 10% PSA.

process; the former cracked during the late phase and collapsed after 1 month. The blended beads containing 20, 40, 60, and 80% PSA decreased in volume over time. Small pieces of the matrix broke off from the surface of the beads containing 100% PSA and, on the sixth day, the beads broke into granules and disappeared gradually.

Results of Ofloxacin Release. The beads with different PSA:PLA ratios showed initial bursts of drug release to differing extents during the first day. Later, the beads containing 100% PLA exhibited a second burst effect on day 33, with the breakdown of the beads. The effective ofloxacin-release periods (>2 μg/mL per day)[12] for beads with different ratios are listed in Table I.

Based on the results of the *in vitro* drug release, and considering synthetic properties such as the stability of form, burst effect, and duration of effective drug release, the authors selected the beads containing 10% PSA as the carrier for ofloxacin in the following experiments. The ofloxacin-release data for beads containing 10% PSA are shown in Figures 1 and 2.

In Vitro Bacteriostasis

The ofloxacin-loaded blended beads containing 10% PSA produced an inhibition zone for *S. aureus*, *E. coli,* and *P. aeruginosa* within the 89 days of the experiment. The overall average diameters of the inhibition zones for the three types of bacteria were 31.8 $\pm$ 2.3 mm, 37.4 $\pm$ 1.9 mm, and 21.2 $\pm$ 3.7 mm, respectively. No inhibition zones for these bacteria were observed for the 10% PSA blended beads without ofloxacin.

In Vivo Drug Release

The beads remained intact during the first 4 weeks of drug release. However, the beads appeared to be reduced to about 50–60% of their original size and were fragile. During the fifth week, the beads broke down into small pieces. From the sixth to eighth weeks, particles of the bead remnants were seen in the bone defects and medullary cavities.

The *in vivo* drug-release data are shown in Table II. During the 8 weeks of drug release, the ofloxacin concentration in the local bone was 20.1 $\pm$ 10.3 μg/g and the ofloxacin concentration in the plasma was 35.6 $\pm$ 18.8 ng/mL.

In Vivo Treatment for Bone Infection

Osteomyelitis Model. In total, three of the osteomyelitis model rabbits died of diarrhea and 17 survived. At 4 weeks after the operative inoculation, the local sites showed a little redness and swelling with an elevated skin temperature, although no fistulae were observed. Inflammatory granulation tissue in response to infection was found in the medullary cavities. Soft tissue abscesses existed near the bone foci in some animals. X-rays of the proximal tibias showed shadows of soft tissue swelling, hyperplastic reactions of the periosteum, and sequestered bone. The bone matrices were uneven, and some areas were sclerotic or had the appearance of low density. Bacterial cultures of all of the specimens and the subsequent latex agglutination tests showed the same strain of *S. aureus* as inoculated. These results provided evidence that the osteomyelitis models had been successfully established.

Efficacy in Osteomyelitis. As a result of the deaths mentioned earlier, the final experimental group consisted of 10 rabbits and the control group consisted of seven rabbits.

The results of the gross observations were as follows. No local signs of infection were observed in the animals in the experimental group. At the termination of the experiment, no soft tissue abscesses or pus in the medullary cavities were found while collecting the specimens. In the control group, the local skin temperature began to increase 2 weeks after the operation. At the end of the experiment, abscesses in the soft tissue were found in six rabbits, and yellow sticky pus was observed in the medullary cavities of all of the control animals.

No roentgenographic signs of osteomyelitis were shown on the X-rays of the experimental group (Figure 3). Roentgenographic changes indicative of chronic osteomyelitis were revealed on the X-rays of the proximal tibia of all of the animals in the control group, with six of them showing shadows of soft tissue abscesses (Figure 4).

The bacterial cultures were all negative for the specimens in the experimental group, whereas every culture of

TABLE II. Ofloxacin Concentrations in Bone and Plasma

	Time (weeks)								
	3/7	1	2	3	4	5	6	7	8
Concentration in bone (μg/g)	46.6	18.8	17.2	13.8	14.7	17.7	14.1	22.6	15.3
Concentration in plasma (ng/mL)	36.8	48.8	52.0	64.3	44.7	26.1	12.1	7.9	27.3

$n = 2$ for every time point.

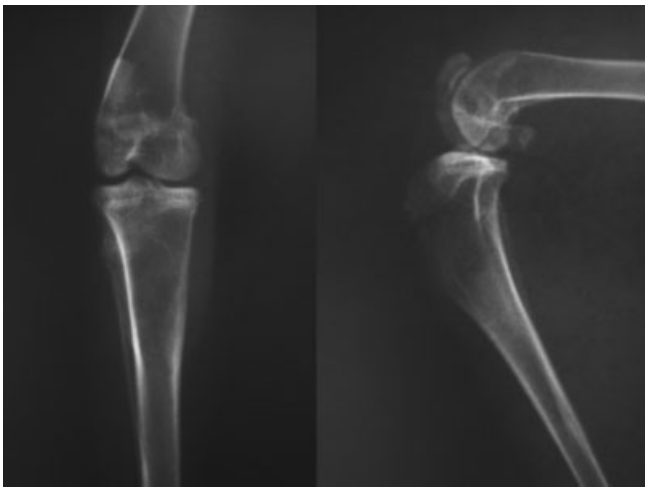

Figure 3. No roentgenographic signs of chronic osteomyelitis were shown in the experimental group 6 weeks after bead implantation.

the specimens in the control group was positive for the inoculated strain of *S. aureus*.

The histological study revealed some tiny focuses of tissue necrosis in the medullary cavity of the specimens in the experimental group, and the particles of the drug-release matrix were found to be surrounded by a thin layer of fibrous tissue (Figure 5). The other structures were relatively normal. No gram-positive or gram-negative bacteria were found. In the control group, large amounts of tissue necrosis and pus were present within the medullary cavity, and necrotic sequestra were shown. Numerous gram-positive *S. aureus* were seen in every specimen (Figure 6).

DISCUSSION

PLA and polyanhydrides are two categories of man-made high molecular weight biomaterials, both of which possess good biocompatibility. They can be normally metabolized

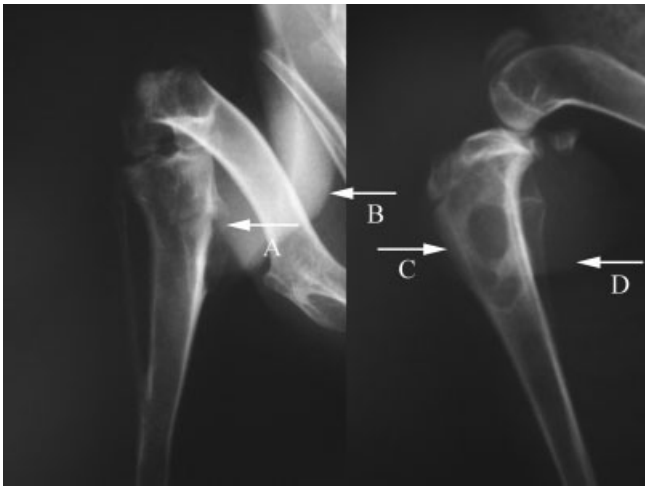

Figure 4. Roentgenographic signs of chronic osteomyelitis (arrow A and C) and soft tissue abscess (arrow B and D) were shown in the control group 6 weeks after the operation.

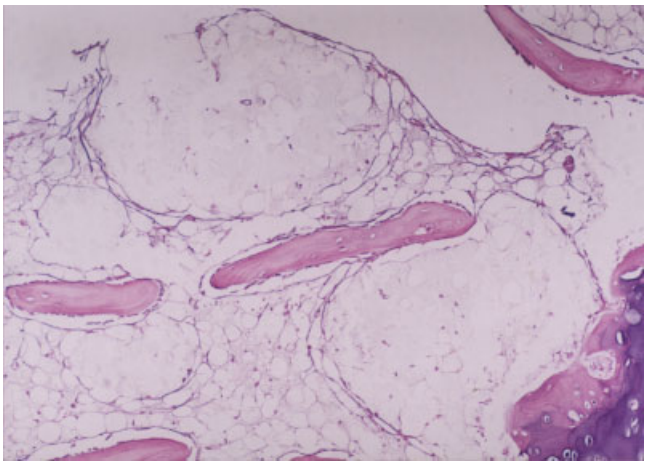

Figure 5. Particles of the drug-release matrix were found surrounded by a thin layer of fibrous tissue in the medullary cavity in the experimental group (HE, 100×). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

and eliminated by the human body.[9,13,14] For decades, PLA has been experimentally and clinically studied in depth as a material for use in surgical bone fixation, and as a carrier for local drug delivery.[3,9,15] Polyanhydrides are a new type of polymer for local drug release, which researchers have made great efforts to investigate during recent years.[4,8] Up to now, however, the combined use of two blended polymers as a carrier for local drug delivery has not been reported. Our present results demonstrated that blending the two types of polymer, which possess different degrading speeds, into a drug-release carrier was feasible. Moreover, we showed that the duration of the overall degradation and the drug release could be controlled, to a certain extent, by simply adjusting the ratio between the two elements. The results of the *in vitro* drug release showed that PSA was completely degraded within 6 days, and that the duration of

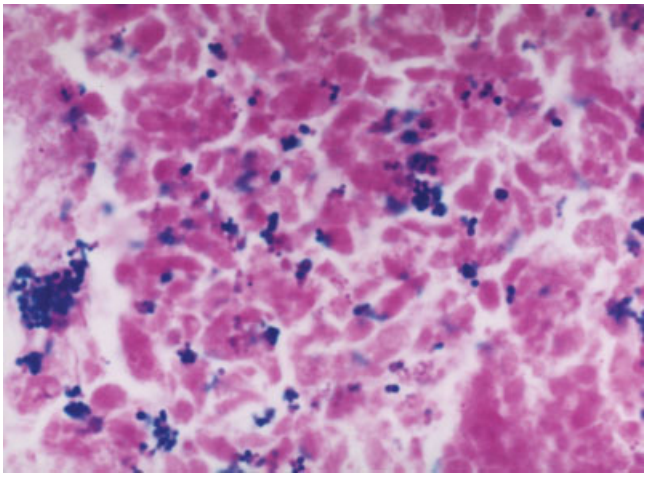

Figure 6. Numerous gram-positive staphylococci were found in the necrotic tissue in the medullary cavity in the control group (crystal violet-phloxine Gram stain, 1000×). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

effective drug release by PLA was 68 days. Blending the two polymers at various ratios into a drug-loading matrix efficaciously regulated and controlled the duration of ofloxacin release from 6 to 68 days. The *in vitro* bacteriostasis experiment, the *in vivo* drug release and the *in vivo* action against bone infection further demonstrated that the ofloxacin-loaded PSA/PLA blends possessed good drug-release properties and antibacterial activities. In comparison with the copolymer synthesis of polylactide/polyglycolide or polyanhydrides, blending two biodegradable polymers to act as a drug-release carrier might greatly simplify the fabrication procedure for the drug-loading matrix, as the polymer blends had similar effects to the copolymers.

Since the successful use of PMMA-gentamycin beads in preventing and treating musculoskeletal infection was reported by Klemm[2] in 1980, a great variety of bone substitutes and biodegradable materials have been studied as potential carriers for use in local antibiotic delivery for bone infection prophylaxis or for the treatment of chronic osteomyelitis; good results have been achieved both experimentally and clinically.[3,8,9,16–19] Among the carriers, some matrixes have the capability of osteoconduction. This not only allows high concentrations of antibiotics that act only locally, but also allows new bone formation at the same time.[17,20–23] Thus, the need for secondary bone grafting could be reduced. A local antibiotic-delivery system has advantages over the systemic administration of antibiotics, in that it can produce high local concentrations with long-lasting durations and low systemic levels of antibiotics without producing toxicity or other adverse effects; in addition, much smaller doses of antibiotics are required for local administration.[3,7,8] Our results were in agreement with these findings. The ofloxacin concentration in the local bone was of the order of micrograms whereas that in the plasma was of the order of nanogram. At the end of the eighth week of local drug release, the ofloxacin concentration in the local bone was still far higher than the minimal inhibitory concentration against *S. aureus* (0.5 μg/mL).[24] Furthermore, the *in vitro* drug release showed that changing the ratio between the two polymers within the bead could regulate the speed of ofloxacin release.

The criterion used to determine the occurrence of osteomyelitis or bone infection in the current research was the possession of at least two of the following three items: first, roentgenographic signs of osteomyelitis shown on X-rays, such as bone destruction, bone necrosis and hyperplastic reaction of the periosteum; second, a positive culture in the medullary cavity, showing the inoculated *S. aureus* strain; and third, histological evidence of osteomyelitis (e.g., bone necrosis, bone abscess, or numerous inflammatory cells) or the presence of bacteria. The criterion for determining the cure of osteomyelitis was that all of the three items must be negative.

Based on the surgical debridement, the ofloxacin-loaded PSA/PLA beads were found to cure the model osteomyelitis in rabbits. This was the direct result of a sustained high concentration of ofloxacin in the medullary cavity, because of the drug release from the beads. At 3 days after the implantation of the beads, ofloxacin content in the local bone was 46.57 μg/g. Later, between the first and the eighth week, the ofloxacin concentration in the bone was maintained at 13.75–18.79 μg/g. Within the duration of the drug release, the range of ofloxacin concentrations was 27.5–93.1 times the minimal inhibitory concentration for *S. aureus*.[24] These ensured the need for the eradication of local bacteria.

In humans, the peak drug concentration in plasma caused by the oral administration of 400 mg ofloxacin is 2.9 μg/mL, while that caused by intravenous administration of the same dose is 4.0 μg/mL.[12,24] As the concentrations of fluoroquinolones exceed their serum concentrations only in the prostate, kidney and lung, and not in the bone,[12,25] it can be theoretically speculated that the peak concentration in the human bone should not exceed that in the plasma under routine conditions. Thus, the local ofloxacin concentration caused by the sustained drug release in our research far exceeded the possible drug concentration in the bone caused by the systemic administration of ofloxacin in humans. Moreover, in the case of chronic osteomyelitis, the possible drug concentration in the bone provided by systemic administration should be lower than the normal concentration, owing to bone devascularization, sequestra formation and the surrounding avascular fibrous tissue.

In the *in vitro* study, the effective ofloxacin-release duration for beads containing 20% PSA was 18 days; this was estimated for the prophylaxis of bone infection in an open fracture after thorough debridement. The higher burst effect during the first day might play an active role in eradicating pathogens in a contaminated wound in the early stages.

Our current results indicated that blending two categories of biodegradable polymers to act as a drug carrier could be a potentially effective method for clinical local drug release.

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DOI 10.1002/jbmb