



## Inhibition of Chronic Osteomyelitis using Sustained Release of Drug from Biodegradable Polymeric Chip

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### Clinical Image

Despite the recent advances in medical and surgical therapies, the treatment of chronic osteomyelitis (bone and joint infection), especially the treatment of Methicillin-Resistant Staphylococcus Aureus (MRSA) osteomyelitis, still remains challenging and is associated with high recurrence rate, morbidity and substantial healthcare cost [1,2]. Current treatment of chronic osteomyelitis primarily involves the surgical debridement of diseased bone tissue followed by long term systematic antibiotic therapy. Poly(methyl methacrylate) (PMMA) beads impregnated with vancomycin, gentamicin or tobramycin have been used commonly for many years as main stream local delivery vehicle in osteomyelitis treatment [3]. However, PMMA beads cannot be degraded or absorbed in the body and it must be removed in a second operation along with its suboptimal release profile with meager 25% to 50% of the antibiotic can be eluted in 4 weeks time, which is far away from being a controlled antibiotic drug delivery carrier [4]. Biodegradable polymer based devices can provide a more controlled release profile and eliminate the utmost need for the additional (removal) surgery of conventional carrier. An ideal antibiotic vehicle should be such that it can improve the therapeutic efficacy of the antibiotic drug and provide a sustained but prolonged release at the site of infection without any local or systematic toxicity while it should be bioadsorbable [5-7]. Recently, we have developed vancomycin loaded biodegradable polycaprolactone (PCL) chip as a local antibiotic drug delivery vehicle for artificially MRSA-infected osteomyelitis which shed light on the new treatment of bone infection without second surgery to remove implant [8]. Although vancomycin is considered as an effective antibiotic against MRSA, sufficient dose of pure vancomycin is unable to penetrate efficiently into local sites due to the growth of malformations near the infection sites. The advantage of local antibiotics delivery is to provide a high drug concentration at the infection site for a prolonged period in sustained manner without systemic side effects.

Vancomycin embedded in a polymer chip (5% (w/w) of vancomycin with respect to polymer) has

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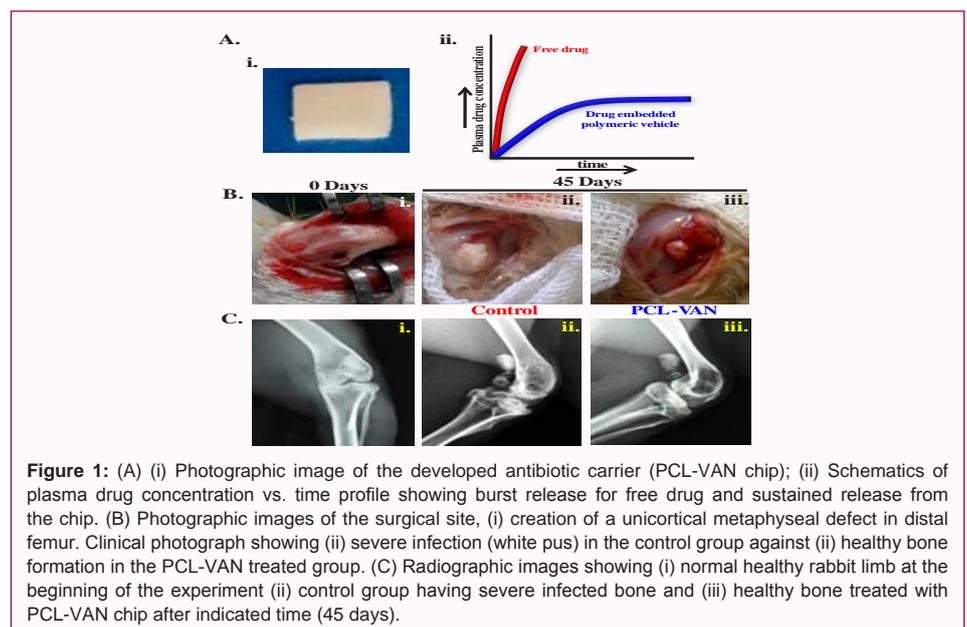
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**Figure 1:** (A) (i) Photograph of the developed antibiotic carrier (PCL-VAN chip); (ii) Schematic of plasma drug concentration vs. time profile showing burst release for free drug and sustained release from the chip. (B) Photographic images of the surgical site, (i) creation of a unicortical metaphyseal defect in distal femur. Clinical photograph showing (ii) severe infection (white pus) in the control group against (iii) healthy bone formation in the PCL-VAN treated group. (C) Radiographic images showing (i) normal healthy rabbit limb at the beginning of the experiment (ii) control group having severe infected bone and (iii) healthy bone treated with PCL-VAN chip after indicated time (45 days).

been developed through solution route, showing sustained release of vancomycin from the chip (Figure 1A). Vancomycin, as an antibiotic, is characterized through MIC in the range of 0.5 to 2  $\mu\text{g ml}^{-1}$  against the MRSA strain [8]. The MIC of the PCL-VAN chip (vancomycin embedded in PCL) is measured to be 1.98  $\mu\text{g ml}^{-1}$  which suggests that the antimicrobial activity against MRSA can well be maintained using PCL-VAN chip. A unicortical defect was created in the metaphysis of the distal femur of healthy male rabbits. A mixed strain of MRSA obtained from a patient suffering from chronic osteomyelitis has been used to induce osteomyelitis at the defect. Rabbits were divided into two groups: Group I (Control) received only free vancomycin while defects in group II were filled with PCL-VAN chips (Figure 1B). Local signs of infection with discharge of pus are observed in all the rabbits of control group. In contrast, suture lines of the limbs are healthy and dry in all the rabbits treated with PCL-VAN chips. Radiographs of control group rabbits exhibit new abscesses, profound cortical reactions and typical signs of osteomyelitis such as osteolysis, sclerosis and sequestrum (Figure 1C). No sign of infection is observed in PCL-VAN treated group instead healthy and recovered bone is noticed clearly suggesting the efficacy of the sustained release along with the bioadsorbability of the chip through biodegradation as required for bone growth. This result illustrates the usefulness of PCL-VAN chip which release the antibiotics within therapeutic levels over a prolonged period and thereby stimulating the antimicrobial activity.

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