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The Sustainable Release of Vancomycin and Its Degradation Products From Nanostructured Collagen/Hydroxyapatite Composite Layers

Tomáš Suchý [1, 2, *], Monika Šupová [1], Eva Klapková [3], Lukáš Horný [2], Šárka Rýglová [1], Margit Žaloudková [1], Martin Braun [1], Zbyněk Sucharda [1], Rastislav Ballay [4], Jan Veselý [2], Hynek Chlup [2], František Denk [1]

[1] Department of Composites and Carbon Materials, Institute of Rock Structure and Mechanics, Academy of Sciences of the Czech Republic, Prague 8, Czech Republic
[2] Faculty of Mechanical Engineering, Czech Technical University in Prague, Prague 6, Czech Republic
[3] Department of Medical Chemistry and Clinical Biochemistry, Charles University, 2nd Medical School and University Hospital Motol, Prague 5, Czech Republic
[4] 1st Department of Orthopaedics, 1st Faculty of Medicine, Charles University in Prague and Motol University Hospital, Prague 5, Czech Republic

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ABSTRACT

Infections of the musculoskeletal system present a serious problem with regard to the field of orthopedic and trauma medicine. The aim of the experiment described in this study was to develop a resorbable nanostructured composite layer with the controlled elution of antibiotics. The layer is composed of collagen, hydroxyapatite nanoparticles, and vancomycin hydrochloride (10 wt%). The stability of the collagen was enhanced by means of cross-linking. Four cross-linking agents were studied, namely an ethanol solution, a phosphate buffer solution of N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride/N-hydroxysuccinimide, genipin, and nordihydroguaiaretic acid. High performance liquid chromatography was used so as to characterize the *in vitro* release rates of the vancomycin and its crystalline degradation antibiotically inactive products over a 21-day period. The maximum concentration of the released active form of vancomycin (approximately 265 mg/L) exceeded the minimum inhibitory concentration up to an order of 17 times without triggering the burst releasing effect. At the end of the experiment, the minimum inhibitory concentration was exceeded by up to 6 times (approximately 100 mg/L). It was determined that the modification of collagen with hydroxyapatite nanoparticles does not negatively influence the sustainable release of vancomycin. The balance of vancomycin and its degradation products was observed after 14 days of incubation.
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Introduction

The infection of implanted endoprostheses represents a serious problem as far as orthopedic and trauma surgery are concerned. Indeed, it is often associated with devastating consequences and treatment presents a substantial challenge for surgeons. Despite the fact that a range of more or less successful methods are available, none of them is considered a method of first choice. One of the ways in which to increase the efficacy of the therapy is to use a local antibiotic delivery system. The local antibiotic treatment of prosthetic joint infection as opposed to the use of systemic antibiotics enjoys the advantage of achieving high antibiotic concentrations, which exceed the minimum inhibitory concentration (MIC) without increasing the level of systemic toxicity. Local carriers of antibiotics used in the field of orthopedics are classified according to composition as synthetic and natural polymers, ceramics, composites, and bone grafts. Since the 1950s, vancomycin (glycopeptide antibiotics) has been used to treat severe infections caused by gram-positive microorganisms. As a result of the increasing incidence of methicillin/oxacillin-resistant *Staphylococcus aureus* in chronically and seriously ill patients, the use of vancomycin has increased significantly. Vancomycin-resistant *Staphylococcus aureus* (VRSA) is most common in elderly patients suffering from leg ulcers or pressure sores, especially those patients with a history of vancomycin-resistant enterococci. One possible explanation as to why infections caused by VRSA are becoming more commonly

* *Correspondence to:* Tomáš Suchý (Telephone: +420266009287).
E-mail address: suchyt@irsm.cas.cz (T. Suchý).

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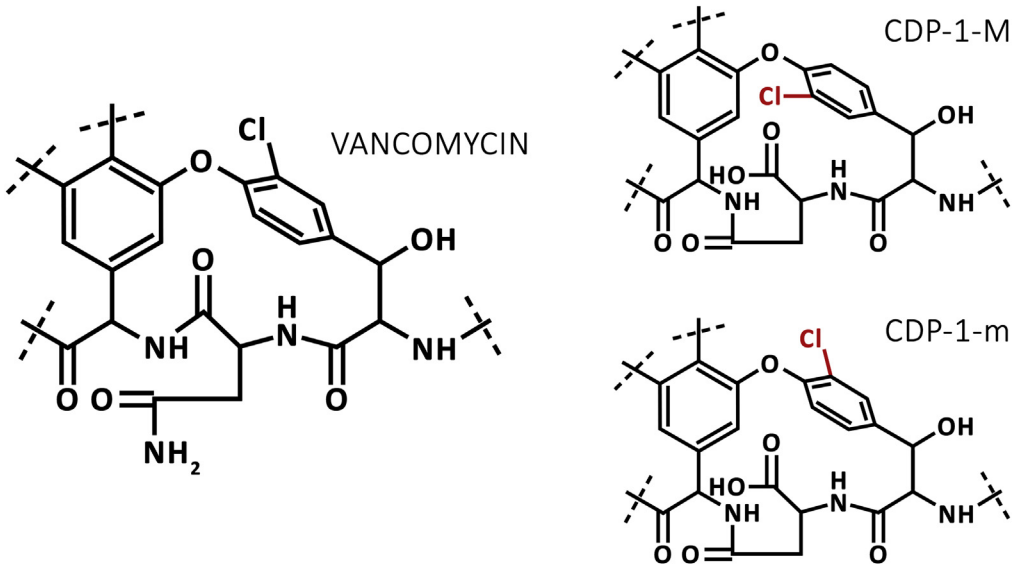

Figure 1. Vancomycin structures and its degradation products.

reported is that vancomycin breaks down over time to form crystalline degradation products (CDP-1s, see Fig. 1), which are devoid of antibacterial activity due to the disruption of the hydrogen bond at the site of the antigen-binding site of a specific vancomycin receptor[1]; at the same time, the efficacy of the active form of vancomycin decreases. During *in vitro* exposure at a temperature of 20°C-25°C, up to 50% of vancomycin is converted to CDP-1s within 16 h and 90% of vancomycin is converted to CDP-1s within 40 h. In addition, an acidic pH of 4.1-4.2 contributes toward the formation of CDP-1s, 2 CDP-1 isomers of which exist: CDP-1M (major) and CDP-1m (minor), conformational isomers, formed by the hydrolytic loss of ammonia. CDPs are structurally similar to vancomycin, that is, they exhibit 2 carboxyl groups. The accumulation of CDP-1s can lead to toxic tissue damage and may also result in the failure of therapy because of the occurrence of subtherapeutic levels of vancomycin.

Polymethylmethacrylate (PMMA) bone cement is commonly used for the fixation of joint prostheses. In the late 1960s, antibiotic impregnated cement was considered to provide prevention from infection.[2] However, it has since been established that PMMA provides an initial burst release of antibiotics with the larger part of the loaded antibiotic remaining within the cement thus preventing PMMA from providing an effective long-term anti-inflammatory function.[3,4] A further problem consists of the exothermic reaction of the bone cement during its polymerization which, to a significant extent, limits the types of antibiotics that can be effectively incorporated into the cement.[5] Moreover, it may accelerate the conversion of vancomycin into crystalline degradation products and thus lead to a significant decrease in antimicrobial activity. In addition, a number of investigators have demonstrated that biofilm can be easily formed on the surface of antibiotic-loaded cement.[6-8] Thus, with a view to overcoming these disadvantages, the study focuses on the development of a resorbable nanostructured composite layer based on natural and synthetic polymers[4,9] modified by means of calcium phosphate nanoparticles.[10]

The aim of the study was to develop a biodegradable nanostructured composite layer with the controlled elution of vancomycin. It is expected that such a layer will be used particularly in the case of known prosthetic joint infections or as a preventative procedure regarding primary joint replacement in a potentially infected site. The layer will provide a bone/implant (titanium alloy) bioactive interface, which will enhance the physiological healing process, will be capable of filling bone defects, and will act as a powerful antibacterial agent against those microorganisms susceptible to vancomycin. The layer is composed of collagen (type I, isolated from calf skin), hydroxyapatite (HA) nanoparticles, and vancomycin hydrochloride. The material composition of the various layers imitates the composition of real bone tissue. Three different layer compositions were analyzed, the aim of which was to verify the potential effect of HA on the release of vancomycin. However, it is important to mention at this point that the application of collagen in the field of tissue engineering is limited because of its poor mechanical properties, high rate of swelling in water, low structural stability, and low resistivity against the enzymatic degradation of its untreated form.[11] A number of cross-linking agents can be used to both improve its mechanical properties and slow down the biodegradation rate of collagen-based materials. Chemical cross-linking is achieved principally through covalent amine/imine linkage. The cross-linking agents and conditions used in this study include N-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (EDC)/N-hydroxysuccinimide (NHS),[12] genipin (GEN),[13] and nordihydroguaiaretic acid (NDGA),[14,15] all of which are commonly used cross-linking agents. The structural properties, swelling ratio, and degradation rate of these scaffolds were investigated in detail and subsequently compared to determine the optimal cross-linking conditions. The study aimed principally to verify whether the local concentration of the vancomycin released exceeded the MIC for VRSA >16 mg/L and to monitor the concentrations of active forms of vancomycin and its degradation products released from the nanostructured composite layer used as local antibiotic carriers in the treatment of osteomyelitis. The objective evaluation of antibiotically active and antibiotically inactive forms of vancomycin is a very important issue. Moreover, crystalline degradation products cross-react with certain immunoassays that use polyclonal antibodies thus resulting in falsely elevated results.[16] High performance liquid chromatography (HPLC) provides an effective tool for the quantitative and qualitative analysis of vancomycin and CDP-1s. At the end of the 1990s, Backes et al.[16] developed an HPLC method to quantitate vancomycin and CDP-1s in the serum of renal patients. However, their method has not been adapted to studies which deal with the evaluation of local vancomycin carriers. The monitoring of the

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