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Hydroxyapatite porous scaffold engineered with biological polymer hybrid coating for antibiotic Vancomycin release

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The purpose of this study is to improve hydroxyapatite (HA) porous scaffolds via coating with biological polymer-HA hybrids for use as wound healing and tissue regeneration. Highly porous HA scaffolds, fabricated by a polyurethane foam reticulate method, were coated with hybrid coating solution, consisting of poly(ε-caprolactone) (PCL), HA powders, and the antibiotic Vancomycin. The PCL to HA ratio was fixed at 1.5 and the drug amounts were varied [drug/(PCL + HA) = 0.02 and 0.04]. For the purpose of comparison, bare HA scaffold without the hybrid coating layer was also loaded with Vancomycin via an immersion-adsorption method. The hybrid coating structure and morphology were observed with Fourier transformed infrared (FT-IR) spectroscopy and scanning electron microscopy (SEM). The effects of the hybrid coating on the compressive mechanical properties and the *in vitro* drug release of the scaffolds were investigated in comparison with bare HA scaffold. The PCL-HA hybrid coating altered the scaffold pore structure slightly, resulting in thicker stems and reduced porosity. With the hybrid coating, the HA scaffold responded to an applied compressive stress more effectively without showing a brittle failure. This was attributed to the shielding and covering of the framework surface by the coating layer. The encapsulated drugs within the coated scaffold was released in a highly sustained manner as compared to the rapid release of drugs directly adsorbed on the pure HA scaffold. These findings suggest that the coated HA scaffolds expand their applicability in hard tissue regeneration and wound healing substitutes delivering bioactive molecules.

1. Introduction

Over the last a few years, the field of *Tissue Engineering* (TE) has expanded noticeably due to the increasing demands of artificial tissues and organs [1]. A multitude of biological materials, such as bioactive ceramics and degradable polymers have been developed and designed to fulfill the requirements for specific uses [2]. The bioactive ceramics, such as calcium phosphates and silica or phosphate-glasses, are considered useful for hard tissue regeneration due to their physicochemical similarity to teeth and bones [3–6]. In oral, maxillofacial, and orthopaedic applications, hydroxyapatite (HA) ceramics have been used mainly as non-load-bearing parts in the form of powders and granules [2, 3], or else, as composites with resins and polymers, offering systems with good osteoconductivity and bioactivity [7, 8]. Compared to dense bodies or granules, the porous scaffolds are highly attractive for their biological benefits, such as osteoconductivity and fast bone ingrowth, due to high surface area and sufficient blood circulation [4, 5]. However, the intrinsically poor mechanical properties of HA, such as low compressive strength and fracture toughness restrict its application only to small sizes of granules and powders or non-load bearing implant [2, 3]. In order to expand its applicability in hard tissue applications, the brittleness of HA needs to be overcome.

The biological performance of HA can be improved by the administration of drugs, such as antibiotics, antitumor, and growth factors [9, 10]. The encapsulated drugs enhance the wound healing and tissue regeneration. Several trials have been made to entrap drugs within the HA ceramic, but the drug release was quite abrupt within initial short periods, hence a sustained release of drug was difficult to obtain [11–13].

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TABLE I Drug amounts loaded onto the scaffolds without and with coating layer. Data were normalized to scaffold weight

Bare scaffold			Coated scaffold		
Designation	Bare *L*	Bare *H*	Designation	Coat *L*	Coat *H*
Initial drug addition (mg/ml DW)	0.01	0.02	Initial drug addition (mg/mg HA-PCL)	0.02	0.04
Total released drug (mg/ml PBS/mg, $\times 10^{-5}$)	0.747	1.53	Coating weight gain (mg/mg graft)	0.057	0.058
Drug loading (mg/mg graft, $\times 10^{-3}$)	1.44	2.92	Drug loading (mg/mg graft, $\times 10^{-3}$)	1.14	2.32

In this respect, the authors engineered HA porous scaffolds to retain enhanced mechanical stability and encapsulate drug more efficiently, by means of coating with a biological polymer. Poly(ε-caprolactone) (PCL) was chosen since it is an FDA cleared polymer, cost efficient and biodegradable [14]. The PCL modified scaffold is expected to overcome its brittleness to some extent. Moreover, the PCL is easily moldable at room temperature, facilitating encapsulation of drug within the porous network. As a model drug, Vancomycin was used since it has a broad-spectrum antimicrobial effect and is applied widely in bone and prosthetic devices mainly to protect against Gram-positive staphylococcal infections [15]. Moreover, in order to maintain the osteoconductivity of the HA porous scaffold, an HA powder was combined with the PCL. The mechanical properties and drug release profiles of the coated scaffold was compared with bare HA scaffold.

2. Materials and methods

2.1. Preparation of HA porous scaffold

The HA porous scaffold was fabricated by a polyurethane foam reticulate method as described in previous work [5]. In brief, commercially available HA powder (Sintering grade, Plasma Biotal, UK) and 6% triethyl phosphate (Aldrich, UK) were mixed in distilled water (DW), and 6% polyvinyl butyral (Aldrich, UK)-water solution was added to make a viscous HA slurry (HA/DW = 0.5 mg/ml). A polyurethane foam template (45 ppi, Customs Foam Systems Ltd., Canada) was replicated by immersing into the slurry, drying, and heat-treating at 600 °C for 3 h and subsequently at 1300 °C for 3 h. The HA scaffolds with two different porosities (~86 and 82%) were prepared by repeating the replication cycles. Porosity was calculated by measuring the dimension and weight of specimen as well as by the Archimedes method ($n = 3$).

2.2. Drug loading in bare HA scaffold

In order to load drugs in the bare HA scaffold, Vancomycin hydrochloride (Sigma, UK) was dissolved in distilled water at different concentrations (Vancomycin/water = 0.01, 0.02 mg/ml). The scaffold, prepared in a dimension of ~10 × 10 × 5 mm, was immersed into the drug-containing solutions for 24 h at room temperature. The ratio of scaffold to water was fixed at 5 mg/ml. The drug amount loaded was determined by measuring the drug amount released completely from the scaffold using a UV spectrophotometer (Unicam, UV500, ThermoSpectronic, UK), and data were represented after normalizing to the initial scaffold weight (Table I).

2.3. PCL-HA hybrid coating and drug loading

The coating process was based on our previous report [16]. In order to make a drug-containing coating solution, firstly, Vancomycin was dissolved in dichloromethane at different concentrations (Vancomycin/solvent = 0.02, 0.04 mg/ml). Within the solution, poly(ε-caprolactone) (PCL, $M_w = 80.000$, Aldrich, UK) was dissolved at PCL/solvent = 0.05 g/ml and the mixture was stirred for 2 h. HA powder (Biotal, UK) was added to the solutions containing drug-PCL, and the mixture was stirred for 24 h (PCL/HA = 1.5 g/g). The HA scaffold was dipped into the solution, rotated, and dried for 72 h under vacuum at room temperature. The weight gain during the coating process was measured. The drug amount loaded in the sample was estimated from the weight change during the coating process and the Vancomycin initially added, and data were represented after normalizing to the initial scaffold weight (Table I). Special care was taken that comparable amounts of drugs were loaded in the bare- and coated-scaffolds by controlling the initial drug additions.

2.4. Characterization and mechanical tests

The morphology of the coated scaffolds was evaluated using scanning electron microscopy (SEM; Stereoscan S90, Cambridge Ltd., UK). The coating structure was analyzed using Fourier transformed infrared (FT-IR; System 2000, Perkin Elmer, USA) spectroscopy. Compressive mechanical tests were performed on scaffolds of a dimension ~5 mm × 10 mm × 10 mm using an Instron (Model 4505, UK) at a crosshead speed of 2 mm/min. The stress-strain curve was obtained, and the compressive strength and elastic modulus were determined from the maximum load recorded and the initial slope of the curve (<2% strain). The capacity of energy absorption (W_{ab}) of the coated and bare scaffolds was defined as the energy necessary to deform a specimen to a strain (ε), and was calculated from the area under the stress-strain curve at a given strain, as follows [17].

$$W_{ab}(\varepsilon) = \int_0^{\varepsilon} \sigma(\varepsilon')\, d\varepsilon'$$

Six samples were tested for each condition, and data were analyzed statistically using Student t test and significance was considered at $p < 0.05$.

2.5. Drug release tests

In order to determine the drug release profile, the bare- and coated-scaffolds were immersed into a glass bottle containing 20 ml phosphate buffered saline (PBS, Aldrich, UK) medium at 37 °C and pH 7.4. At predetermined time periods, the samples were taken out, and the drug released in the medium was quantified using a UV spectrophotometer at a wavelength of 280 nm. A calibration curve was obtained with Vancomycin concentrations in the range of 0.2–15 (μg/ml), in which the curve was linear with a relationship of absorbance = 113.36 × concentration (mg/ml) following Beer's law [18]. Special care was taken that the concentration of released drug lay within the calibrated range by diluting the solution with additional PBS if required. Using the relationship, the absorbance measured in the test was directly converted to an apparent drug release after dividing the drug release by the initial scaffold weight (mg/ml/mg scaffold). The apparent drug release was also normalized to the drug amount initially loaded within the coating to observe the relative amount of the drug release. The *in vitro* drug release tests were performed in triplicate, and data were represented as mean ± one standard deviations (1SD).

3. Results and discussion

3.1. Coating morphology and structure

The SEM morphologies of the porous scaffolds without and with PCL-HA hybrid coating are represented in Fig. 1(A)–(C). The bare HA scaffold, obtained by a polyurethane reticulated foam method, exhibited a well-developed open pore structure (Fig. 1(A)). The porosity and average pore size were approximately 86% and 500–700 μm, respectively. When a PCL-HA hybrid was coated on the scaffold, the pore structure changed slightly. The stems became thicker and some pores were partially closed (Fig. 1(B)). The porosity of the coated scaffold decreased slightly (83%). At high magnification, the coating layer was somewhat rough but uniformly covered the scaffold surface throughout (Fig. 1(C)). The drug Vancomycin might be adherent to the HA powders or dispersed in the PCL film.

The coating structure was evaluated with FT-IR spectroscopy and is shown in Fig. 2. Data on pure PCL and HA powders are represented as references (Fig. 2(C) and (D), respectively), and data on the hybrid coating without drug (Fig. 2(B)) is also measured to observe the effect of drug on the coating structure. The hybrid coating loaded with drug (Fig. 2(A)) represented mixed bands typical of HA (P-O at 580, 600, 980–1050 cm^{-1} and O─H at 630 cm^{-1}) and PCL (C═O at 1770 cm^{-1}, C─H at 1250–1400 cm^{-1}, and C─O at 1050–1180 cm^{-1}) as also seen in HA and PCL references (Fig. 2(C) and (D), respectively). The drug-free coating sample showed little difference, confirming that the drug had no significant chemical effect on the coating structure (Fig. 2(B)). Moreover, when compared to the peaks of HA and PCL references, those of the hybrid coating did not shift, suggesting no chemical reaction between HA and PCL components. Based on the FT-IR spectroscopic data, it was concluded that the coating components were mixed physically, without any significant chemical reactions. These morphological and compositional features of the coating layer were similar to our previous report on HA-PCL containing Tetracycline drug [16]. Compared to small pore size seen in the previous study (150–200 μm), the larger pore size (500–700 μm) used in this study allowed the scaffold to be coated more uniformly without pore clogging [16].

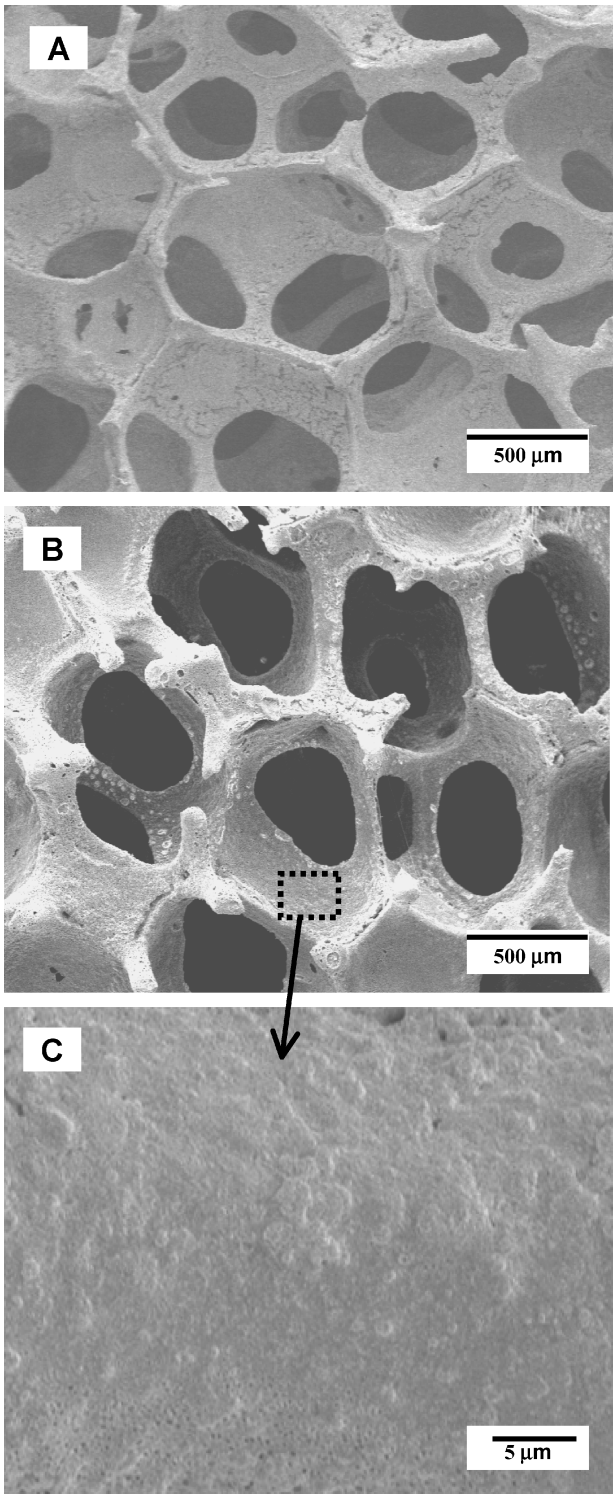

Figure 1 SEM morphologies of the HA porous scaffolds without (A) and with (B and C) hybrid coatings.

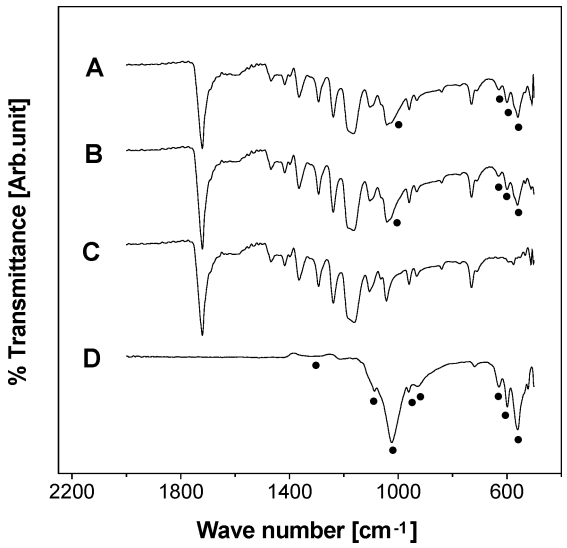

Figure 2 FT-IR spectroscopies of the PCL-HA hybrid coating layer with (A) and without (B) Vancomycin drug: Data on pure PCL (C) and HA (D) were represented as references. Symbol (●) represents HA related bands, others peaks are from PCL.

3.2. Mechanical properties

Through the hybrid coating, the mechanical properties of the scaffold changed. The stress-strain curves of the scaffolds were monitored under a compressive load at a constant speed, as shown in Fig. 3. Bare HA scaffolds with different porosities (86 and 82% in Fig. 3(A) and (B), respectively) were compared with a coated sample (83% in Fig. 3(C)). Both bare scaffolds exhibited a typical failure mode for brittle ceramics, i.e., catastrophic failure after a maximum stress [19]. The scaffold of a low porosity had a higher maximum stress, but the trend of the stress-strain curve was similar. In contrast to the bare sample, the coated scaffold did not show an abrupt failure but instead, the stress increased sharply above the strain of ∼0.6. Such behavior, known as 'densification', is usually observed in metallic or polymeric

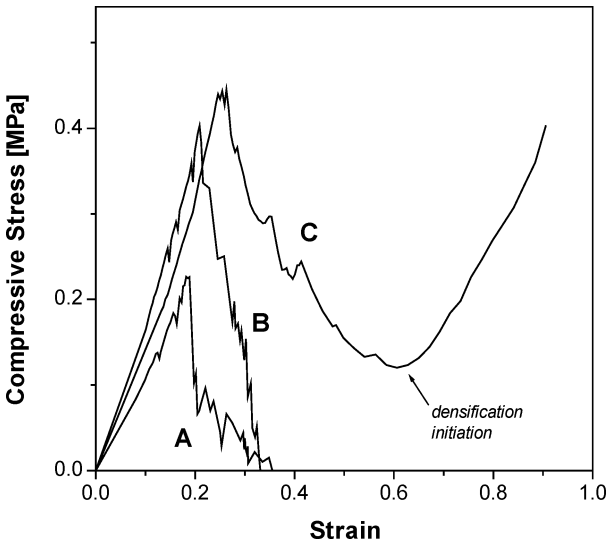

Figure 3 Stress-strain curves of the HA porous scaffolds without (A, B) and with (C) hybrid coatings. Porosity of bare-HA was 86 (A) and 82% (B), and that of coated one was 83% (C). The bare-HA scaffolds showed a catastrophic failure; whilst the coated one didn't show a final failure, rather it showed a densification at a strain of about 0.6.

TABLE II Summarizing the mechanical properties of the porous scaffolds without and with hybrid coatings. ($n = 6$, mean ± SD). Data significantly higher ($p < 0.05$) with respect to bare scaffold of low porosity 86% (*) and high porosity 82% (**)

Mechanical properties	Bare scaffold		Coated scaffold
	Porosity 86%	Porosity 82%	porosity 83%
Compressive strength (MPa)	0.21 (±0.05)	0.41* (±0.07)	0.45* (± 0.06)
Elastic modulus (MPa)	0.83 (±0.09)	1.36* (± 0.24)	1.32* (±0.16)
Energy absorption (Ncm)	1.89 (± 0.48)	3.08 (±0.88)	6.69** (± 0.70)

foams, which undergo a considerable degree of plastic deformation [20]. With the aid of the polymer hybrid coating layer, the HA ceramic also underwent this kind of deformation in response to an applied load. The mechanical properties of the scaffolds without and with coatings are summarized in Table II. The compressive strength and elastic modulus were obtained by the maximum stress and the initial slope (<2% strain), respectively, from the stress-strain curves. Between the bare scaffolds, as expected, the sample with lower porosity had significantly higher strength and elastic modulus ($p < 0.05$) [5]. The coated scaffold also had a slightly higher strength and elastic modulus compared to the bare sample with higher porosity (significant at $p < 0.05$), but both mechanical properties were similar to those of the bare sample with corresponding porosity. From these results, it is believed that the strength and elastic modulus of the scaffold were mainly affected by the porosity reduction rather than by the coating layer itself. This observation on the porosity effect also supports our previous work on the HA scaffold with higher porosity [16].

However, as was observed in Fig. 3, the stress-strain curves between the coated and bare scaffolds were quite different. The coated sample did not show fracture, but instead underwent densification. The energy absorption capacity (W_{ab}) of the scaffolds was calculated from the area under the stress-strain curve at a given strain and the specific volume of scaffolds, and is represented in Fig. 4. The bare scaffolds showed limited energy absorption until fracture (∼0.3–0.4 strain), as shown in Fig. 4(A)–(B). In contrast, the coated sample absorbed energy far away to the densification point (∼ 0.6 strain), as shown in Fig. 4(C). The total energy absorbed by the coated scaffold (∼6.7 N·cm) was over twice as that of the bare sample (∼3.08 N·cm) with a similar level of porosity (significant at $p < 0.05$). Although there was little increase in the elastic modulus and strength as a result of applying the hybrid coating compared to bare scaffold with similar porosity, the energy absorption capacity of the former was improved considerably.

At a low compression load, the bare HA framework can sustain the load by means of dissipating energy to neighboring stems, but under higher compression, the brittle stem is not flexible enough to resist the load and a fracture initiates from a weaker stem, leading finally to collapse. However, in the coated scaffold, the coating solution, having migrated into pore channels and

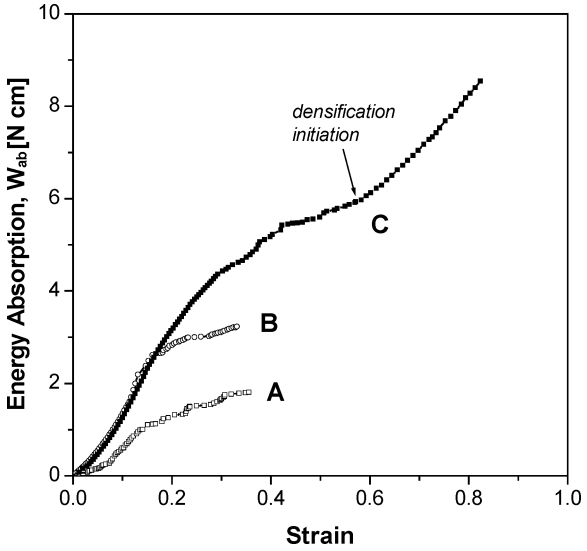

Figure 4 Energy absorbed by the porous scaffolds in response to an applied load: Bare-HA with porosity 86 (A) and 83% (B), and coated HA (C). Data, obtained with the stress-strain curve in Fig. 4, was calculated from the area under the stress-strain curve at a given strain.

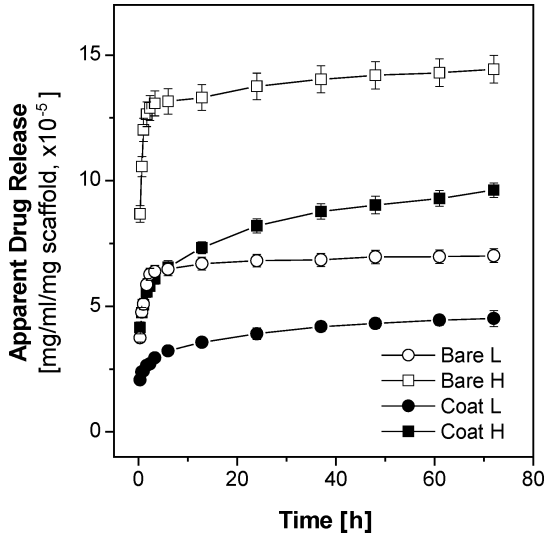

Figure 5 Apparent Vancomycin drug release amounts from the bare and coated HA porous scaffolds after release test in a PBS solution at 37 °C for periods up to 3 days. Each scaffold was loaded with drugs at two different amounts (low '*L*' and high '*H*').

covered the micropores and flaws, allows the stems to maintain a much higher load before catastrophic fracture [21, 22]. Although the maximum strength of the bare HA with lower porosity (83%) was improved, such effective energy absorption was not observed. Based on these results, the application of a PCL-HA coating to HA scaffold provides enhanced flexibility of the scaffold. Moreover, the coating parameters, such as concentration, composition, and biopolymer type, can be controlled and modified for further development of the system.

3.3. Drug release profiles

Within the coating layer of the scaffold, Vancomycin was loaded via the coating process to investigate the efficacy of the coated scaffold for a drug delivery system. Bare HA was also loaded with Vancomycin by incubating the HA in a Vancomycin containing solution. Fig. 5 shows the apparent drug amount released from the bare and coated scaffolds. Two different amounts of drug (high '*H*' and low '*L*') were loaded initially in both scaffolds. The bare HA scaffolds showed abrupt drug release within short periods and plateaued thereafter. The drug amount released in the sample at high drug loading (bare *H*) was doubled compared to that at low drug loading (bare *L*), but the overall trend was similar. However, the coated scaffolds released drugs much more slowly. Although the initial release was high, the rate was slowed down with time.

These different drug profiles were well illustrated in Fig. 6, when plotted after normalizing the apparent release amount to the initial drug loadings. The release amounts at short (1 h) and prolonged (72 h) periods in Fig. 6 are summarized in Table III. Data show clearly different release profiles between coated and uncoated samples, and little difference was observed with regard to drug loading amounts. Compared to the abrupt initial burst (as high as ∼70–80%) in bare HA samples, the

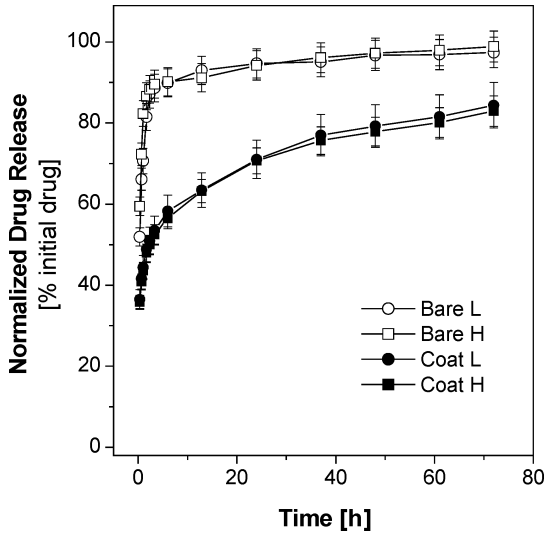

Figure 6 Normalized drug release amounts from the bare and coated HA porous scaffolds with respect to initial drug amounts loaded.

coated ones showed much lower initial burst (∼44%). Moreover, while almost 90% of the drugs in the bare HA were released within a day (24 h), the drugs entrapped within the hybrid coatings were released in a controlled manner over a 3-day period. Such a release profile observed in the coated scaffolds could provide a rapid delivery of drug to give antibacterial effects at the wound site and a further sustained release to aid long-term healing.

TABLE III Drug release amounts from the bare and coated scaffolds after initial (1 h) and prolonged (72 h) periods

	Drug release amount (% initial drug)			
Release period (h)	Bare *L*	Bare *H*	Coat *L*	Coat *H*
1	70.6	82.3	44.4	43.6
72	97.4	98.8	84.4	82.9

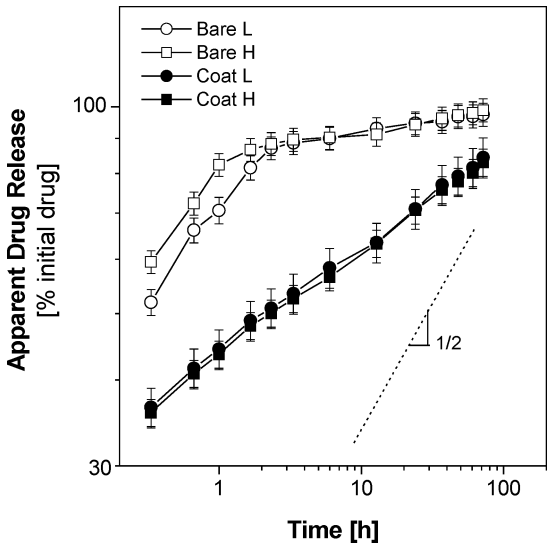

Figure 7 Log-log plot of the normalized drug release amounts from the bare and coated HA porous scaffolds with respect to initial drug amounts loaded. Dotted line represents a reference slope (1/2) when diffusion controlled.

The normalized drug release amounts were plotted on a log-log scale, as represented in Fig. 7. The bare HA samples showed a two-step release pattern. The first rapid step was due to the loosely bound drugs on the surface, and the second reduced stage resulted from the drugs, whether tightly bound or entrapped within micropores of stems. In contrast, the coated ones showed a one-step linear relationship, suggesting that the drug release mechanism in the coated samples is uniform throughout the periods.

The drug loaded in bare HA showed a much more reduced release rate at prolonged period after the abrupt release, following a linear fit in log-log plot. However, the release amount in this regime was extremely low, that is, about 90% of the loaded drug was released within 24 h and only 10% of it was released over 3 days. As a local drug delivery, this release profile is not so satisfactory.

The encapsulation of drug within the coating layer diminished the initial abrupt release which was observed in the bare samples (∼70–80%). The initial release (∼44%) in the coated samples was attributed to the drug not being encapsulated efficiently, as was observed in our previous report on Tetracycline drug [16]. Like other polyester biopolymers, such as poly lactic-/glycolic-acid, the PCL is quite hydrophobic, so a certain amount of the hydrophilic Vancomycin could not be encapsulated [23] effectively.

The drugs in the coating layer should be released both by coating degradation and diffusion of drugs through the coating layer. Based on the simple release kinetics suggested by Peppas, i.e., the release amount follows a power law of release time, with a power constant lower than 1 (released amount is proportional to time^n, where n is power constant lower than 1) [24]. When the slope of the graph on the coated samples was calculated from the log-log plot, it was lower than the diffusion controlled power constant 1/2. This phenomenon was observed usually in systems, where drugs were released by both diffusion and degradation [25]. In this manner, the HA powder would influence the drug release behavior considerably, because of its high water uptake capacity. The high water uptake of HA would increase the drug release by means of offering water channels for drug diffusion as well as increasing the coating degradation since the PCL polyester is degraded mainly via a hydrolytic process.

In this respect, the coating properties can be controlled physically (coating density, thickness, and morphology) and chemically (composition, HA powder properties, and PCL crystallinity), to provide a more efficient and effective drug release profile to the system. Furthermore, based on the sustained and controlled release of the antibiotic drug, this engineered coating-scaffold system is expected to be used as a delivery carrier of other bioactive molecules, such as growth factors and proteins for enhanced tissue regeneration and wound healing.

4. Conclusions

A scaffold-coating system, porous hydroxyapatite (HA) coated with poly(ε-caprolactone) (PCL) polymer and HA hybrid, was developed for use in hard tissue regeneration. The antibiotic drug Vancomycin was loaded within the coating layer to enhance wound healing as a drug delivery system. When compared to bare HA scaffold, the coated scaffold responded more effectively to an applied compressive load in terms of energy absorption and stress relaxation. The encapsulated drug within the coated scaffold was released in a more sustained and controlled manner as compared to the drug directly adsorbed on the scaffold without the coating layer.

Acknowledgments

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