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Effect of poly lactic-co-glycolic acid encapsulation on drug delivery kinetics from vancomycin-impregnated Ca-Mg silicate scaffolds

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Abstract

The identification of drug delivery mechanisms is critical to design a device that offers a drug release kinetics within the therapeutic window. In this paper, the drug release kinetics of bioresorbable tissue engineering scaffolds coated/uncoated with biodegradable polymer layers is studied. Interconnectedly porous bredigite ($MgCa_7Si_4O_{16}$) scaffolds were fabricated by a sacrificial urethane foam replica method, loaded with vancomycin hydrochloride ($C_{66}H_{75}Cl_2N_9O_{24}$) and then encapsulated in poly lactic-co-glycolic acid (PLGA, LA/GA=50:50) coatings of two different thicknesses. Field-emission scanning electron microscopy (FESEM) and Fourier-transform infrared spectroscopy (FTIR) were used to verify the macroporous morphology and chemical constituents of the devices. The release profiles of vancomycin from these systems into phosphate buffered saline (PBS) at 37 °C were also recorded by ultraviolet-visible (UV-VIS) spectroscopy. To explore the dominant drug delivery mechanisms, the experimental data of the drug release was then fitted with several drug delivery mathematical

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models, including the Higuchi, Hixson-Crowell, Korsmeyer-Peppas, Peppas-Sahlin, Weibull, zero-order and first-order. Comparing the correlation coefficient of the regressions as a measure of goodness-of-fit, it was found that vancomycin release from the bare scaffold is subjected to a dissolution-controlled kinetics, whereas the PLGA-coated scaffolds mainly display a combination of diffusion- and dissolution-controlled mechanisms for the drug release. It can be accordingly concluded that the bredigite scaffolds are a versatile device for different local drug delivery strategies offering rapid, single-stage and dissolution-controlled release kinetics that can be easily modulated into a diffusion-controlled, biphasic and prolonged release through biopolymer coating.

***Keywords*:** Hard tissue regeneration; Aliphatic polyester; Glycopeptide antibiotic; Fickian and non-Fickian transport phenomena; Biomedical applications

1. Introduction

Recently, there have been significant advances in the area of bioceramic tissue engineering scaffolds. The progress in the field has prompted the fabrication of porous three-dimensional matrixes that not only provide a structural sustenance for the regenerated tissue but also can act as a platform for controlled local delivery of various therapeutics. In this regard, bioresorbable ceramic scaffolds have been used as implantable carriers of numerous drugs and formulations, including antibiotics (e.g. vancomycin [1] and cefazolin [2, 3]), growth factors (e.g. BMP-2 [4, 5] and VEGF [6, 7]) and nonsteroidal anti-inflammatory drug (e.g. Ibuprofen [8, 9] and diclofenac [10, 11]).

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An efficient local drug delivery device should be able to provide a certain release kinetics within the therapeutic dosage of the incorporated agent. Therefore, to predict and modulate the drug release kinetics, it is crucial to determine underlying mechanisms by which the loaded drug is leached-out of the matrix. Mathematical modeling is one of the useful tools in the characterization of experimental drug release profiles by defining a relation between the properties of the carrier system as a function of release time. In the design of systemic or local drug delivery systems, these models enable the evaluation of contributing transport phenomena in the release process *in vitro* and *in vivo* and allow the optimization of underlying parameters that affect the release kinetics [12]. Generally, physical mechanisms that govern the drug release behavior of a system are categorized into diffusion, dissolution, degradation, partitioning, osmosis, matrix swelling and erosion [13]. Dependent on the properties of the carrier system, a combination of the aforementioned phenomena can contribute to different release profiles.

Post-surgery bacterial infections, which originate mainly from environmental contaminations or opportunistic bacteria residing in the patient's body, are prone to cause severe complications in regard to the medical implants and scaffolds. Thus, addressing the issue is a priority in the design of implantable therapeutic-loadable devices. In local drug delivery approaches, antibiotic loaded polymethyl methacrylate (PMMA) spacer beads have been most prominently used for countering post-surgery infections [14, 15]. However, there are drawbacks in the application of PMMA beads, including their non-resorbable nature that demands secondary surgeries for removal [16]. Calcium phosphates and bioactive glass materials have been also studied as matrixes for local delivery of antibiotics. Hydroxyapatite (HA), a well-known calcium phosphate which is characterized by its slow bioresorption rate and relatively

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poor mechanical properties, has been used in local delivery of different antibiotics in the form of scaffolds and pellets [1, 17]. Magnesium-calcium silicates are another class of bioresorbable ceramics that offer better mechanical properties and osteoinduction compared to other prominent bioceramics [18-20]. The presence of Mg in the structure of these ceramics promotes faster bone mineralization and regeneration as well as a decreasing risk of osteoporosis [21, 22]. Bredigite ($Ca_7MgSi_4O_{16}$), a member of this family of bioceramics, exhibits excellent bioresorbability and bioactivity. In this study, a bredigite scaffold impregnated with a model antibiotic, vancomycin, was focused on as a matrix of local drug delivery for infection prophylaxis. Vancomycin is a glycopeptide antibiotic that kills bacterial cells by inhibiting peptidoglycan biosynthesis [23]. Vancomycin acts via binding to the terminal D-Ala-D-Ala dipeptide of bacterial cell wall precursors, thereby impeding the further function of these intermediates into peptidoglycan [24, 25].

In order to effectively combat the bacterial proliferation and infection at the implanted site, the local drug delivery device should counter the possible initial post-surgery bacterial contamination and also remain effective against opportunistic systemic bacteria that could lead to infections in longer periods. Therefore, it is crucial for these devices to provide a sustained dosage of the loaded therapeutic exceeding the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of the agent [26-28]. To achieve this goal, the modulation and control of the drug release rate form the matrix are necessary. One of the promising approaches to control the release rate is the encapsulation of the matrix in biodegradable polymers. Poly lactic-co-glycolic-acid (PLGA) and polycaprolactone (PCL) are two of the most common degradable polymers applied for this purpose as they have excellent

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biocompatibility [29], display a successful modulation of drug release [30], cause a minimal inflammatory response during degradation [31] and produce biocompatible byproducts [32]. However, PCL has a slower degradation compared to PLGA [33] and suppresses bredigite bioresorbability. Thus, PLGA was chosen as the coating material on bredigite scaffolds to control the drug release behavior in this study.

Experimental data of vancomycin release from the bare and PLGA-coated bredigite scaffolds, with two different thicknesses, was obtained by UV spectrometry and then fitted with the kinetics models of Korsmeyer-Peppas, Peppas-Sahlin, Higuchi, Weibull, Hixson-Crowell, zero-order and first-order. To the best of the authors' knowledge, this work is the first mathematical study which integratedly employs all of these aforementioned models to detail, as a case study, vancomycin release from Mg-containing silicate-based tissue engineering scaffolds coated with a biodegradable polymer comprehensively. The understanding gained from the mathematical description of the drug release profile is helpful to determine the device design parameters that affect the drug release behavior and thus can provide a powerful tool to predict the performance and efficacy of different drug-device combinations based on bredigite scaffolds.

2. Materials and methods

2.1. Materials

The materials used in this study were tetraethyl orthosilicate ($(C_2H_5O)_4Si$, TEOS, Merck, Germany, Purity>98%), nitric acid (HNO_3, Merck, Germany, 2 M), magnesium nitrate hexahydrate ($Mg(NO_3)_2.6H_2O$, Merck, Germany, Purity>98%), calcium nitrate tetrahydrate ($Ca(NO_3)_2.4H_2O$, Merck, Germany, Purity>98%), polyurethane foam (density: 25 ppi, porosity

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>97%), sodium alginate (Sigma Aldrich, Germany, Purity>98%), PLGA 5004A (LA/GA = 50:50, the intrinsic viscosity of 0.4 dl/g, acid-terminated, M_w = 44 kDa, acid number: min 3 mg KOH/g) and vancomycin hydrochloride ($C_{66}H_{75}Cl_2N_9O_{24}$, Sigma Aldrich).

2.2. Fabrication

For the synthesis of bredigite, the sol-gel process was employed [20, 34]. Briefly, TEOS, H_2O, and HNO_3 were mixed together at the molar ratio of TEOS/H_2O/HNO_3 = 1:8:0.16 and hydrolyzed for half-hour under constant stirring. The process was followed by adding $Mg(NO_3)_2.6H_2O$ and $Ca(NO_3)_2.4H_2O$ into the solution and stirring for 5 h at room temperature. Thereafter, the solution was maintained at 60 °C for 24 h and dried at 120 °C for 48 h. The obtained powder was calcined at 700 °C for 3 h.

To fabricate interconnectedly porous bredigite scaffolds, the sacrificial foam replication method modified according to Ref. [18] was used. A homogeneous slurry was obtained by suspending the calcined powder in the pre-prepared sodium alginate aqueous solution (3 wt%). Thereafter, polyurethane foam templates were impregnated with the slurry, then dried at 60 °C overnight and finally heated at 300 °C for 1 h and at 1350 °C for 3 h to remove the polymeric struts and to perform the sintering process, respectively.

For vancomycin loading into the scaffolds, the drug was first dissolved in distilled water at the concentration of 0.3 mg/ml. Then, the sintered scaffolds were immersed in the drug solution at a scaffold-to-solution ratio of 5 mg/ml for one day and then dried at room temperature.

For PLGA coating of the vancomycin-loaded scaffolds, they were immersed into the pre-prepared PLGA-acetone solutions (concentrations of 5 and 10% w/v, dipping time = 3 sec,

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solution volume for each sample = 10 ml), centrifuged at 300 rpm for 5 sec to remove the excess solution and heated at 60 °C for 2 h to remove the polymer solvent.

2.3. Structural characterization

Field-emission scanning electron microscopy (FESEM, MIRA3 TESCAN, Czech Republic) was used to analyze the structure of the bare and coated scaffolds. To confirm the incorporation of vancomycin into the devices and also to investigate any possible interactions between the drug and device constituents, Fourier-transform infrared spectroscopy (FTIR, Thermo Nicolet, Avatar, USA) was also carried out. In this regard, the vancomycin-loaded PLGA-coated scaffolds were mechanically powdered using a mortar and pestle for 10 min. Thereafter, FTIR was conducted in a spectral range of 4000-400 cm^{-1} with the spectral resolution of 4 cm^{-1} at room temperature and a moisture-free environment.

2.4. Drug release study

To achieve the profiles of vancomycin release *in vitro*, each of the bare, 5% PLGA-coated and 10% PLGA-coated scaffolds was individually immersed in 20 ml of phosphate buffered saline (PBS) at pH of 7.4 and 37 °C with three repetitions. The ratio of the scaffolds to PBS was 4 mg/ml. At specified time intervals, aliquots of 3 ml were extracted from each sample and replaced with 3 ml of the fresh PBS solution. The level of vancomycin released into the PBS medium was measured by a UV spectrophotometer (UV–1100, MAPADA INSTRUMENT, Shanghai, China) at the wavelength of 280 nm. Furthermore, the total amount of the drug entrapped into the devices was measured after the scaffolds were completely degraded in the

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medium, which was used to calculate the accumulative percentage of the drug release. The calibration curve was obtained in the vancomycin concentration range of 0.001-0.02 mg/ml with the correlation coefficient of $R^2 = 0.99$, where the calibration curve followed the beer's law [35]:

$$A = 1.9 \times C \quad (1)$$

where A is the absorbance (counts) and C is the concentration (mg/ml) of vancomycin.

2.5. Drug release kinetics models

To study the mechanism of vancomycin release from the bare and PLGA-coated bredigite scaffolds, the experimental release data were regressed with several relevant kinetics models. To find the best fit between the experimental data and models, the nonlinear least-squares curve-fitting technique was employed, where the criterion of goodness-of-fit was considered in terms of the closeness of correlation coefficient (R_c) to the unit. The used models included:

Higuchi: the Higuchi kinetics model is derived from the Fick's law of diffusion and can be used to describe drug release profiles from various carrier systems due to its simplicity [36]:

$$\frac{M_t}{M_{\inf}} = k_H \sqrt{t} \quad (2)$$

where M_t and M_{inf} denote the cumulative drug release at the time t and infinite, respectively, and k_H is a kinetics constant influenced by the diffusion coefficient of the drug in the carrier along with other specific parameters of the carrier.

Hixson-Crowell: This model can be used for drug carriers that display a dissolution-controlled mechanism and is defined by the following equation [37]:

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$$\sqrt[3]{1-\frac{M_t}{M_{\inf}}} = -k_{HC}t \tag{3}$$

Korsmeyer-Peppas: This kinetics model can be used in drug delivery systems that exhibit purely Fickian diffusion transport, non-Fickian Case II transport as a result of matrix erosion/degradation or a combination of both the mechanisms [37]:

$$\frac{M_t}{M_{\inf}} = k_{KP}t^n \tag{4}$$

where k_{KP} is a constant that depends on the structure and geometry of the carrier system and n is a diffusional exponent by the value of which the discernment of dominant release mechanism becomes possible.

Weibull: The Weibull function has long been employed in the study of drug release kinetics and like Korsmeyer-Peppas can discern the dominant release mechanism between diffusion and Case II transport [38]:

$$\frac{M_t}{M_{\inf}} = 1-\exp\left(-at^b\right) \tag{5}$$

where a is a constant and b is a shape parameter according to the value of which distinguishing the dominant release mechanism is possible.

Peppas-Sahlin: this model is used to determine the contribution of diffusion and erosion mechanisms in systems with anomalous transport (a combined action of both the mechanisms) [12].

$$\frac{M_t}{M_{\inf}} = k_1t^{0.5} + k_2t \tag{6}$$

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where k_1 and k_2 are constants descriptive of diffusion and erosion contributions, respectively. The contribution of diffusion (F) to the drug release can be obtained by the following equation:

$$F = \frac{1}{1+\frac{k_2}{k_1}t^{0.5}} \tag{7}$$

Also, the ratio of the dissolution (D) to diffusion (F) contributions can be also calculated as follows:

$$\frac{D}{F} = \frac{k_2}{k_1}t^{0.5} \tag{8}$$

First-order and zero-order: these kinetics models are descripted, respectively, as follows [39]:

$$\ln\left(1-\frac{M_t}{M_{\inf}}\right) = -k_{FO}t \tag{9}$$

$$\frac{M_t}{M_{\inf}} = k_{ZO}t \tag{10}$$

It is worth noting that all of the aforementioned models are valid for fitting up to the first 60% of the drug release, except for the Weibull model which can be applied for the entire drug release range.

3. Results and discussion

Fig. 1 shows the FESEM micrograph of the bare and PLGA-coated bredigite scaffolds. Based on Fig. 1a, the bare scaffold exhibits a uniformly macroporous structure of high interconnectivity, which is essential for bone tissue engineering applications. Struts of this

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sample are also characterized by microparticles and nanopores of 1-3 μm and 90-750 nm in size, respectively (Fig. 1b), which act as the matrix of the drug loading. The 5% PLGA coating deposited on the surface of the struts partially fill the micropores and nanopores, while keeping the high interconnectivity of macropores, according to Figs. 1c and 1d. This morphological evolution is continued by increasing the PLGA concentration to 10% (Figs. 1e and 1f), where a relatively smooth surface is formed on the strut surfaces in the sample. It would be worth mentioning that the porosity level of these bare, 5% PLGA-coated, and 10% PLGA-coated bredigite scaffolds are 90.7 ± 0.7, 82.7 ± 2.1, and 77.9 ± 2.4, respectively [18], which are in the suitable range for tissue engineering.

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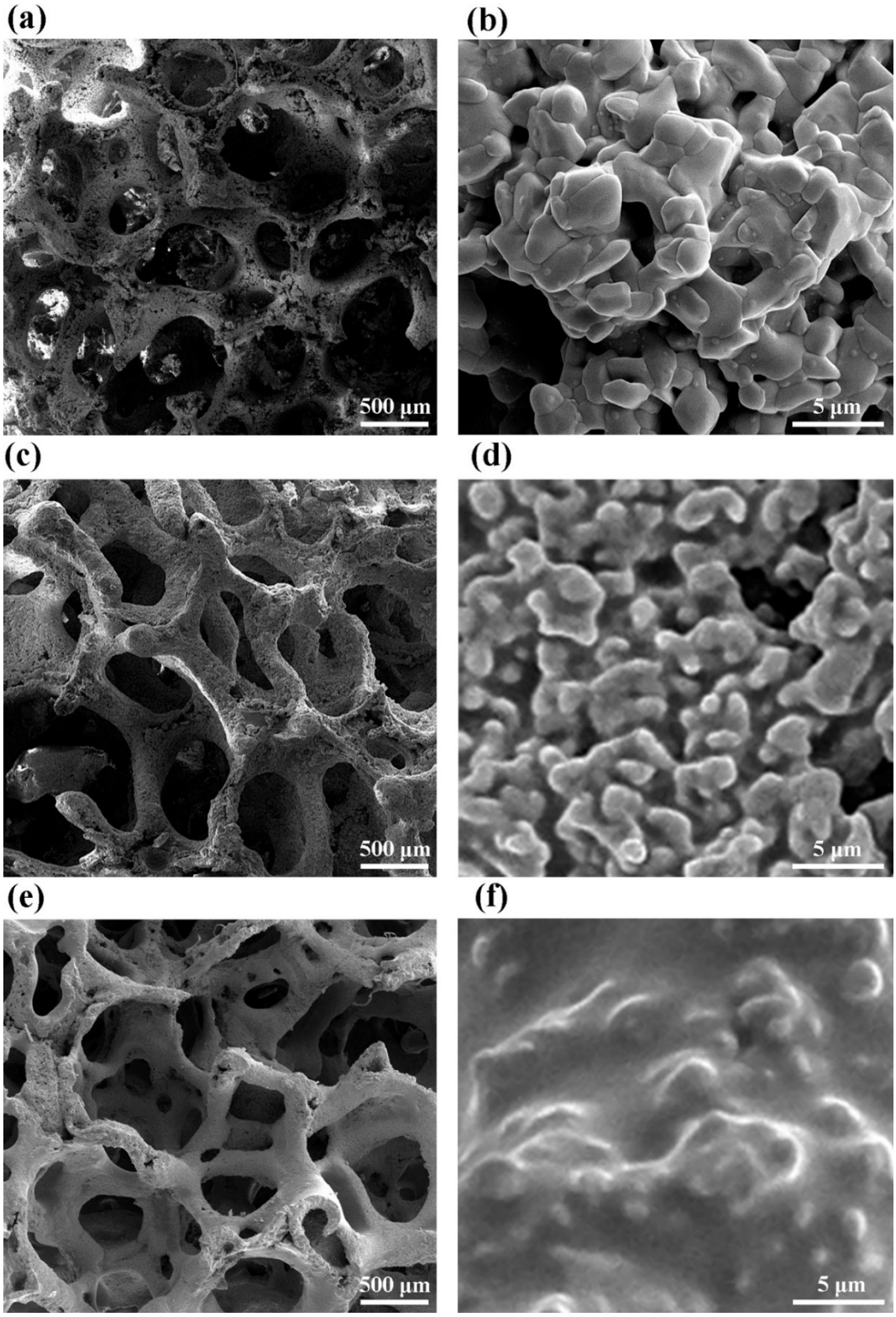

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Fig. 1. FESEM micrographs of the bare (a, b), 5% PLGA-coated (c, d) and 10% PLGA-coated (e, f) vancomycin-loaded bredigite scaffolds in two magnifications.

The FTIR spectrum of the PLGA-coated vancomycin-loaded scaffold and the related bonding assignments are depicted in Fig. 2. Absorption bands at 516, 553 and 616 cm^{-1} are attributed to O–Mg–O bending, Ca–O stretching and O–Si–O bending, respectively. Also, peaks of 1050, 960 and 873 cm^{-1} belong to Si–O tetrahedron stretching. According to the literature [40-42], these bands verify the formation of bredigite. Absorption bands at 3406, 1655, 1504 and 1231 cm^{-1} are also attributed to the vibrational modes of hydroxyl stretching, C=O stretching, C=C and phenols, respectively [43-45], confirming the successful impregnation of the scaffolds with vancomycin. The strong characteristic peak of 1752 cm^{-1} is assigned to C=O stretching. The peaks at 1182 and 1089 cm^{-1} are also attributed to C–O–C stretching, and the vibration mode at 1454 cm^{-1} corresponds to C–H stretching. The recent assignments are in good agreement with the functional groups of PLGA [46-49], verifying the successful encapsulation of the vancomycin-loaded bredigite scaffolds in this aliphatic polyester. Also, the lack of any wavenumber shifts in the absorption bands of vancomycin suggests no chemical interactions between the drug and other substances, which is indicative of the physical incorporation of the drug between the bredigite struts and PLGA layer.

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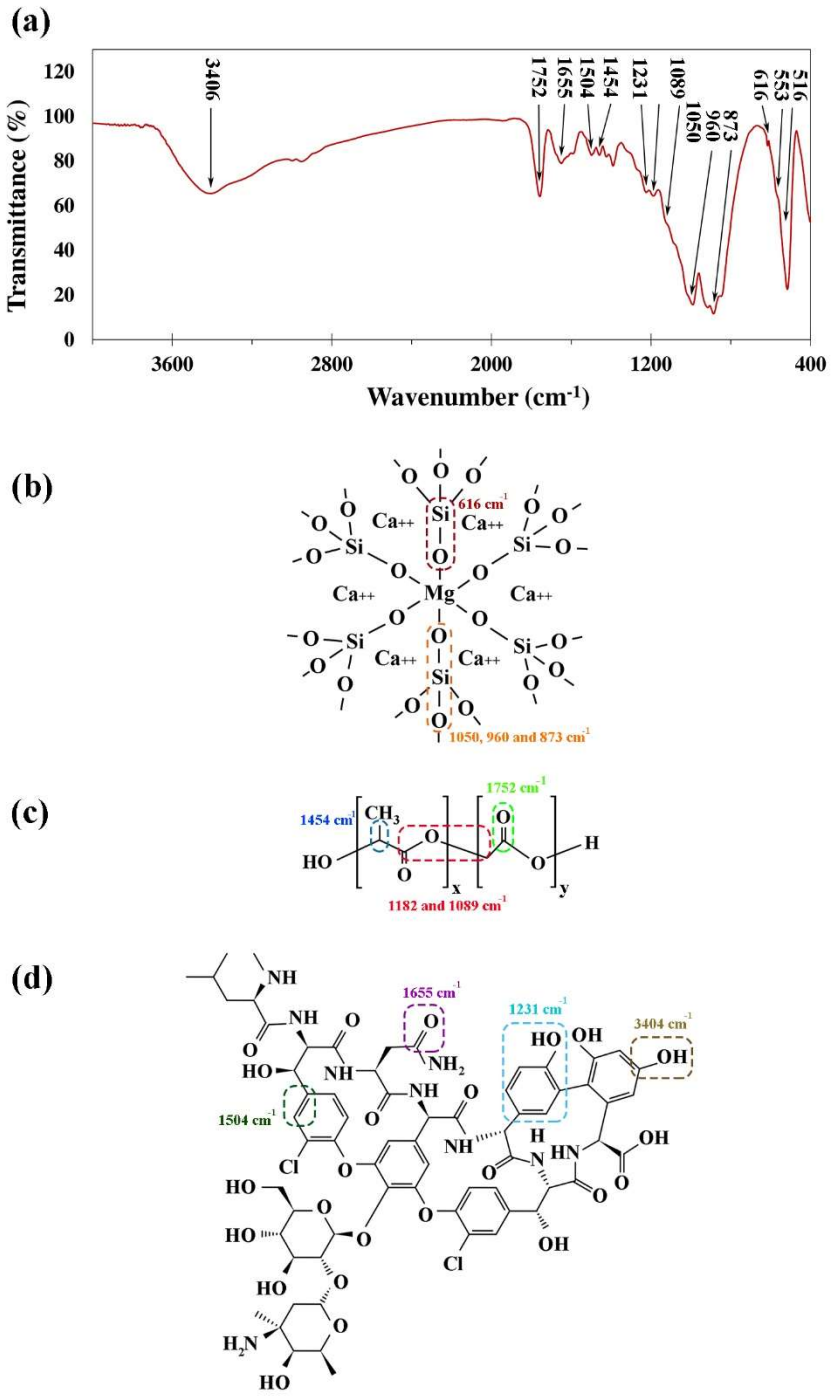

Fig. 2. FTIR spectrum of the 10% PLGA-coated vancomycin-loaded bredigite scaffold (a), part of the bredigite structure including one [MgO_6] octahedron and six surrounding [SiO_4]

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tetrahedra (b), structure of PLGA, where x and y are the numbers of lactic acid and glycolic acid units, respectively (c) and molecular structure of vancomycin hydrochloride (d).

Fig. 3 presents the accumulative percentage of vancomycin released from the scaffolds into the PBS solution. The dependency of the drug release rate on the presence and concentration of the PLGA coatings points out variations in the drug delivery mechanisms controlling the release kinetics. The sharp drug release of the bare sample is compatible with the merely physical adsorption of the drug on the strut surface realized from the FTIR analysis, which is retarded by the PLGA encapsulation providing lower slopes for the drug release profiles.

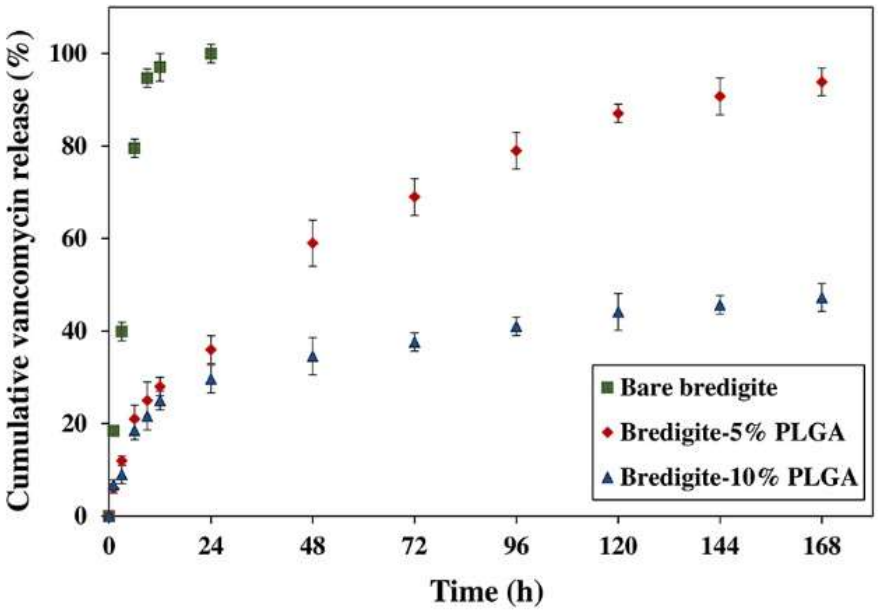

Fig. 3. Cumulative percentage of the drug release from the scaffolds.

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To discern the mechanism of vancomycin release from the scaffolds, fitting of the experimental data with the mathematical models was followed. The Higuchi model (Eq. 2) was the first model considered albeit to the first 60% of release, which is mainly employed to describe diffusion-controlled drug release processes and has been successfully applied for porous ceramic matrixes [50, 51]. The fitting curves and data with regard to this model are revealed in Fig. 4 and Table 1, respectively. The bare scaffold shows a poor fit with the Higuchi kinetics, suggesting that diffusion cannot be solely responsible for vancomycin release from this sample. In contrast, the 5% PLGA-coated sample shows a good fit with this model only in the first burst stage of release which constitutes the first 60% of release. The best fit for the 10% PLGA-coated sample is found when the experimental data is regressed by a two-step approach of 0-12 h and 12-168 h that denote the burst and sustained stages of release. The k_H parameter in the Higuchi model depends directly on the diffusion coefficient of the agent and reversely on the diffusion path length in the barrier. The k_H values obtained by fitting are equal to 7.83 for the 5% PLGA-coated scaffold, and 7.06 and 2.33 for the first and second stages of release for the 10% PLGA-coated sample, respectively. This corroborates that by increasing the PLGA concentration and thereby coating thickness, the efficiency of encapsulation is improved and the drug release rate is decreased as the diffusion of vancomycin is further hampered by the thicker PLGA coating.

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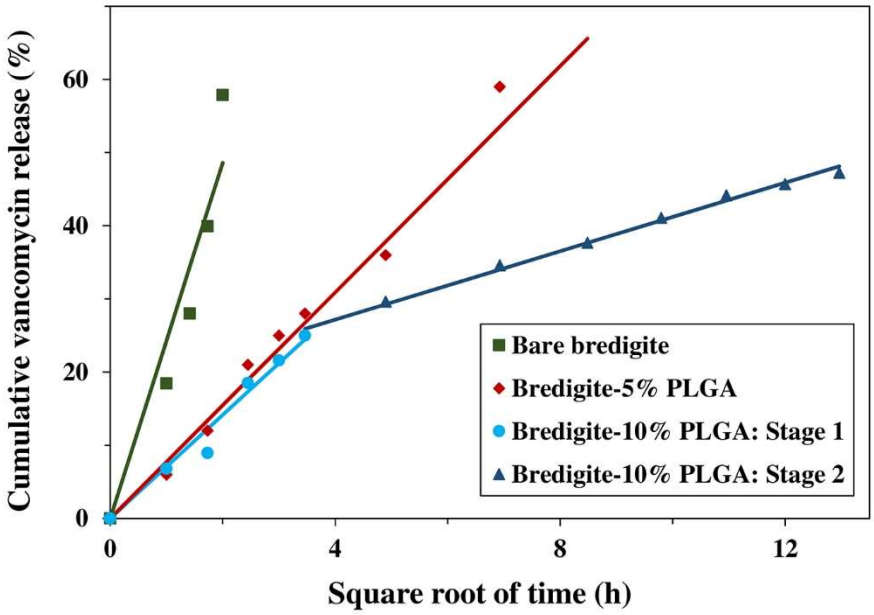

Fig. 4. Fitted Higuchi plot of vancomycin release from the scaffolds.

Table 1. Higuchi fitting parameters of the drug release from the scaffolds.

Sample	Stage 1		Stage 2	
	k_H	R_c	k_H	R_c
Bare bredigite	24.29	0.83	-	-
5% PLGA-bredigite	7.83	0.98	-	-
10% PLGA-bredigite	7.06	0.97	2.33	0.96

The Hixson-Crowell model (Eq. 3) essentially describes carrier systems that release the incorporated drug with a dissolution-controlled mechanism as the carrier itself is continuously dissolved in the surrounding medium while maintaining a constant geometry with decreasing proportional dimensions [37]. The fitting results of the experimental data with this model are

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demonstrated in Fig. 5 and Table 2. The very good fit for the bare sample with R_c=0.98 indicates that the release of vancomycin from this carrier is mainly controlled by a dissolution-based kinetics. This accordingly suggests that the role of bredigite bioresorption in the drug release prevails over the dissociation of van der Waals adsorption bonds of the drug to bredigite, in contrast to non-resorbable and non-degradable carriers that only benefit from the latter contribution to drug delivery [52]. Since the dissolution of bioresorbable ceramics initiates at their surface, it assists the rapid release of adsorbed vancomycin molecules and thereby leads to a burst release. However, the data of the PLGA-encapsulated samples is poorly fitted with the Hixson-Crowell model, verifying the domination of diffusion realized from the Higuchi fits. That is, the PLGA coatings control the fast drug delivery rate of the bredigite scaffolds via a transformation of the dissolution-to-diffusion mechanism.

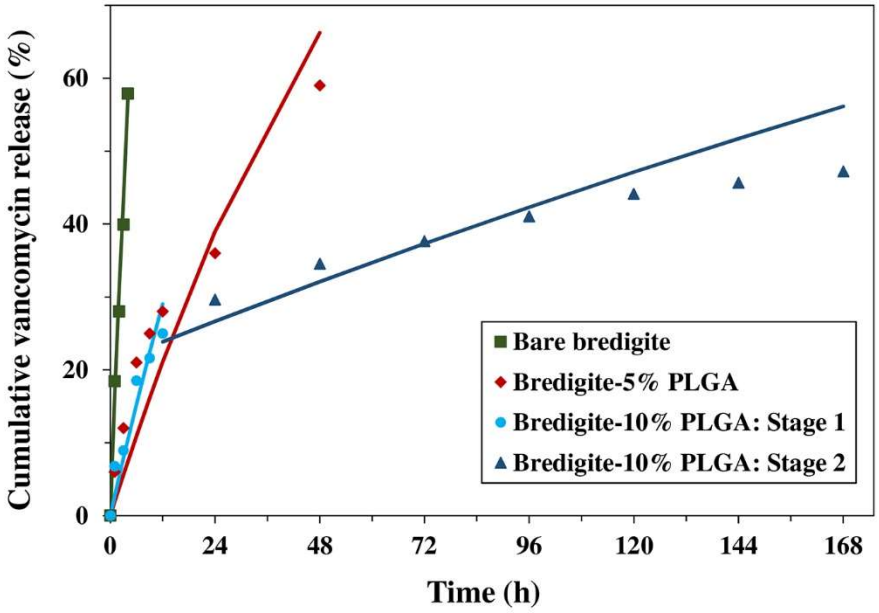

Fig. 5. Fitted Hixson-Crowell plot of vancomycin release from the scaffolds.

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Table 2. Hixson-Crowell fitting parameters of the drug release from the scaffolds.

Sample	Stage 1		Stage 2	
	k_{HC}	R_c	k_{HC}	R_c
Bare bredigite	0.058	0.98	-	-
5% PLGA-bredigite	0.006	0.85	-	-
10% PLGA-bredigite	0.007	0.89	0.001	0.72

To further explore the mechanism of vancomycin release from the samples, the Korsmeyer-Peppas model (Eq. 4) was also used. This well-established model can distinguish the domination of diffusion, dissolution or a combination of them in the drug delivery kinetics, based on the value of *n*. Indeed, the Higuchi model is a special form of the Korsmeyer-Peppas equation, in which the *n* value is equal to 0.5 describing a purely diffusion-controlled mechanism. For the values of $0.5 \leq n \leq 1$, the drug release is considered to be anomalous non-Fickian transport, which can be interpreted as a superposition of both degradation and diffusion mechanisms. Based on Fig. 6 and Table 3, the drug release data of the bare scaffold shows a good fit with this model and gives the *n* value of 0.92, signifying a mixed dissolution- and diffusion-controlled kinetics. The closeness of *n* to the unit as indicative of the absolute domination of dissolution is also compatible with the conclusions of the Higuchi and Hixson fits. The PLGA-coated samples also display a good fit with this model. Typically, the *n* value calculated for the single stage of the 5% PLGA-coated scaffold is equal to 0.54, whereas the two-stage release regression of vancomycin from the 10% PLGA-scaffold gives the *n* values of 0.59 and 0.45 for the first and the second stages, respectively. Therefore, it can be inferred that in the

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single stage of the drug release from the 5% PLGA-coated scaffold, both the out-diffusion of vancomycin molecules and the dissolution of the matrix take place simultaneously, where diffusion is dominant as realized from the Higuchi and Hixson-Crowell fits. This is in good agreement with the fact that PLGA (LA/GA= 50:50) is degraded in a physiological medium by about 2 weeks [53-55] and the level of the polymer degradation is negligible for the shorter periods. The first release stage of the 10% PLGA-coated sample is also similar to the 5% PLGA-coated sample, whereas purely Fickian diffusion occurs in its second stage, based on the *n* values. The reason behind the dependency of mechanism on the PLGA concentration and coating thickness is postulated to be the level of the coating coverage. The 5% PLGA coating partially covers the scaffold struts and pores, which to some extent allows the dissolution-controlled release of vancomycin molecules through uncoated regions similar to the bare sample. On the contrary, the decline of the dissolution-controlled contribution to the drug release for the 10% PLGA-coated sample is attributed to the improvement in the coating coverage.

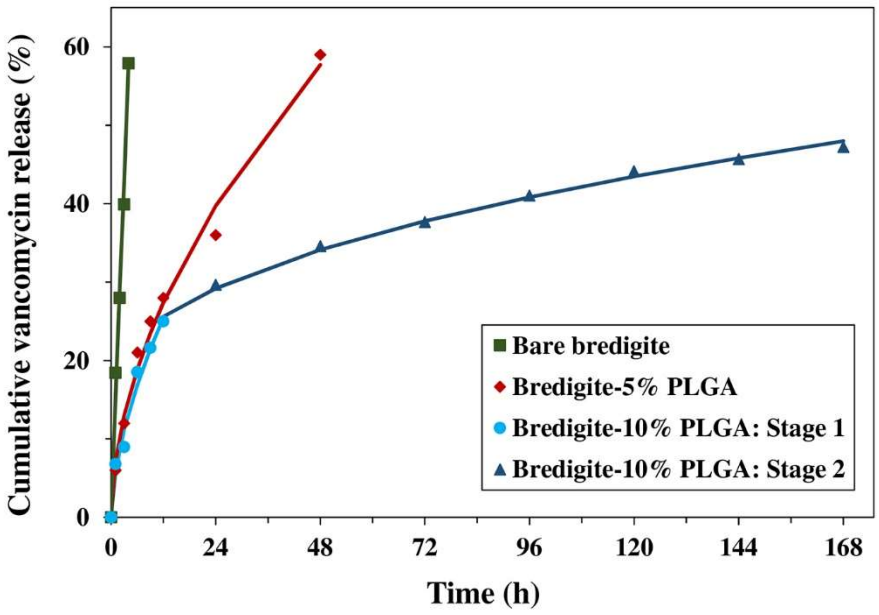

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Fig. 6. Fitted Korsmeyer-Peppas plots of vancomycin release from the scaffolds.

Table 3. Korsmeyer-Peppas fitting parameters of the drug release from the scaffolds.

Sample	Stage 1			Stage 2		
	k_{KP}	N	R_c	k_{KP}	n	R_c
Bare bredigite	15.48	0.92	0.98	-	-	-
Bredigite-5% PLGA	7.17	0.54	0.98	-	-	-
Bredigite-10% PLGA	5.81	0.59	0.98	3.23	0.45	0.99

To further substantiate the above findings, the drug release data was also fitted with the Weibull model (Eq. 5), as signified in Fig. 7. Unlike the other models which are only applicable to the first 60% of the cumulative drug release [56], the Weibull model can be used for the entirety of the release data [38]. The Weibull model used to be criticized for lacking a kinetics basis and its unattributable parameters to physical underlying phenomena [57]. However, Papadopoulou et al. [38] used Monte Carlo simulations to correlate the physical release kinetics to the *b* parameter of the Weibull model and the *n* parameter of the Korsmeyer-Peppas model, enabling the characterization of drug release kinetics by the Weibull model. This model is not limited by the geometry of the matrix as it is applicable in all Euclidian spaces [38]. It has been reported that in the Weibull function, values of $b \leq 0.75$ indicate Fickian diffusion, whereas $0.75 \leq b \leq 1$ signifies a combined mechanism and values of $b \geq 1$ point to a complex release mechanism [38]. Based on Table 4, the value of *b* obtained for the bare bredigite sample is equal to 1.34, where the sigmoid shape of the fitting curve indicates that the rate of release does not

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change monotonically. This means that initially the vancomycin release from the matrix is increased up to a pivot point and thereafter the release rate is decreased. For the 5 and 10% PLGA-coated samples, fitting with the Weibull model gives the *b* values of 0.77 and 0.37, respectively. That is, the 5% PLGA-coated scaffold presents a combined release mechanism throughout the entirety of the drug release, whereas the 10% PLGA coating results in a diffusion-controlled release, which are both in good agreement with the conclusions drawn from the previous models fits. It is well worth to note that when the 10% PLGA-coated sample is analyzed by the Korsmeyer-Peppas model with a two-step regression, the results indicate anomalous and diffusion-controlled transport mechanisms for the first and second stages of release, respectively. However, the fitting of the entire range of the drug release with the Weibull model exhibit an overall diffusion-controlled release mechanism. This discrepancy in the different ranges of the data fitting suggests the diminishing role of the dissolution mechanism for the 10% PLGA-coated sample, where the Weibull model essentially has no ability to distinguish it.

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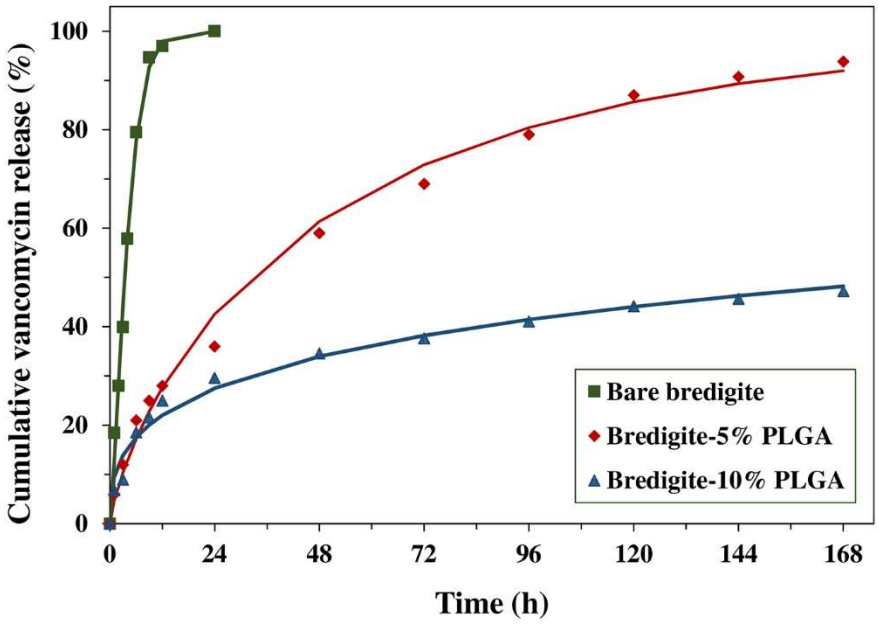

Fig. 7. Fitted Weibull plots of vancomycin release from the scaffolds.

Table 4. Weibull fitting parameters of the drug release from the scaffolds.

Sample	*b*	*a*	R_c
Bare bredigite	1.34	7.70	0.99
Bredigite-5% PLGA	0.77	21.33	0.99
Bredigite-10% PLGA	0.37	10.02	0.99

The Peppas-Sahlin kinetics model (Eq. 6) is essentially used for drug carrier systems that exhibit anomalous transport in the way that it is able to determine the contribution of Fickian and non-Fickian phenomena in the drug release [58]. Accordingly, this fitting is only applied to the first 60% of release for the 5% PLGA-coated sample (1-48 h) and the first release stage of the 10% PLGA-coated scaffold (0-12 h), as recognized by the Korsmeyer-Peppas fitting. The fitting

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curve and data with respect to the Peppas-Sahlin model are presented in Fig. 8 and Table 5, respectively. The drug release data of the 5% PLGA sample was fitted in the two ranges of 0-12 h and 0-48 h, so the former range is used to compare the behavior of the PLGA-coated samples and the latter range is discussed separately in regards to the 5% PLGA-coated sample itself. The first and second terms of the Peppas-Sahlin equation can be obtained by fitting, which denote the diffusion and matrix-dissolution contributions, respectively, as follows.

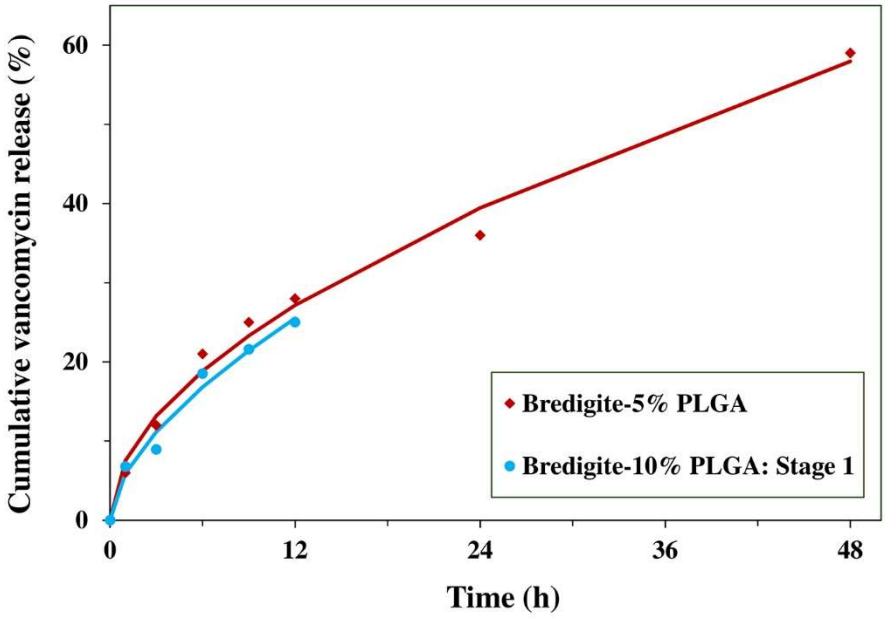

Fig. 8. Fitted Peppas-Sahlin plots of vancomycin release from the 5 (a) and 10% (b) PLGA-coated scaffolds.

Table 5. Peppas-Sahlin fitting parameters of the drug release from the scaffolds.

Sample	k_1	k_2	R_c

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	0-12 h	0-48 h	0-12 h	0-48 h	0-12 h	0-48 h
Bredigite-5% PLGA	5.16	7.53	1.00	0.03	0.99	0.98
Bredigite-10% PLGA	5.50	-	0.54	-	0.98	-

Comparing the magnitude of the k_1 and k_2 values listed in Table 5, it can be understood that the diffusion contribution prevails over dissolution for both the samples. Evidently, the contribution of the dissolution mechanism in the 10% PLGA-coated scaffold is lower than that in the 5% PLGA-coated sample as the polymer coating thickness is increased. In contrast, the contribution of diffusion is greater in the 10% PLGA-coated scaffold, which is logical to assume due the thicker PLGA layer. The plot of D/F calculated for the anomalous transport regions of the PLGA-coated samples, based on Eqs. 7 and 8, is revealed in Fig. 9. For the 5% PLGA-coated scaffold, the ratio is increased from 0.19 at the beginning of release to 0.67 at 12 h (Fig. 9a). This demonstrates the increasing contribution of the matrix dissolution to vancomycin release by increasing the soaking time in PBS. Indeed, the thin PLGA coating of this scaffold provides the greater contribution of the diffusion-controlled leach-out of vancomycin in the initial duration of the release study; however, the penetration of the medium into uncovered pores by progression of immersion increases the contribution of dissolution-controlled release. The first release stage of the 10% PLGA-coated sample (0-12 h) provides up to 25% of vancomycin release with the increase of D/F from 0.09 to 0.34 (Fig. 9a). The lower value of D/F for this sample compared to the 5% PLGA-coated scaffold over the entire range of 0-12 h is indicative of the higher contribution of diffusion, whereas the increasing rate of the dissolution contribution for 10% PLGA-coated sample is lower than that for the 5% PLGA-coated sample. This finding is in

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agreement with the FESEM micrographs of the PLGA-coated scaffolds (Fig. 1), in which it is shown that the 10% PLGA-coated sample benefits from a smoother and better encapsulation of pores in the polymer coating.

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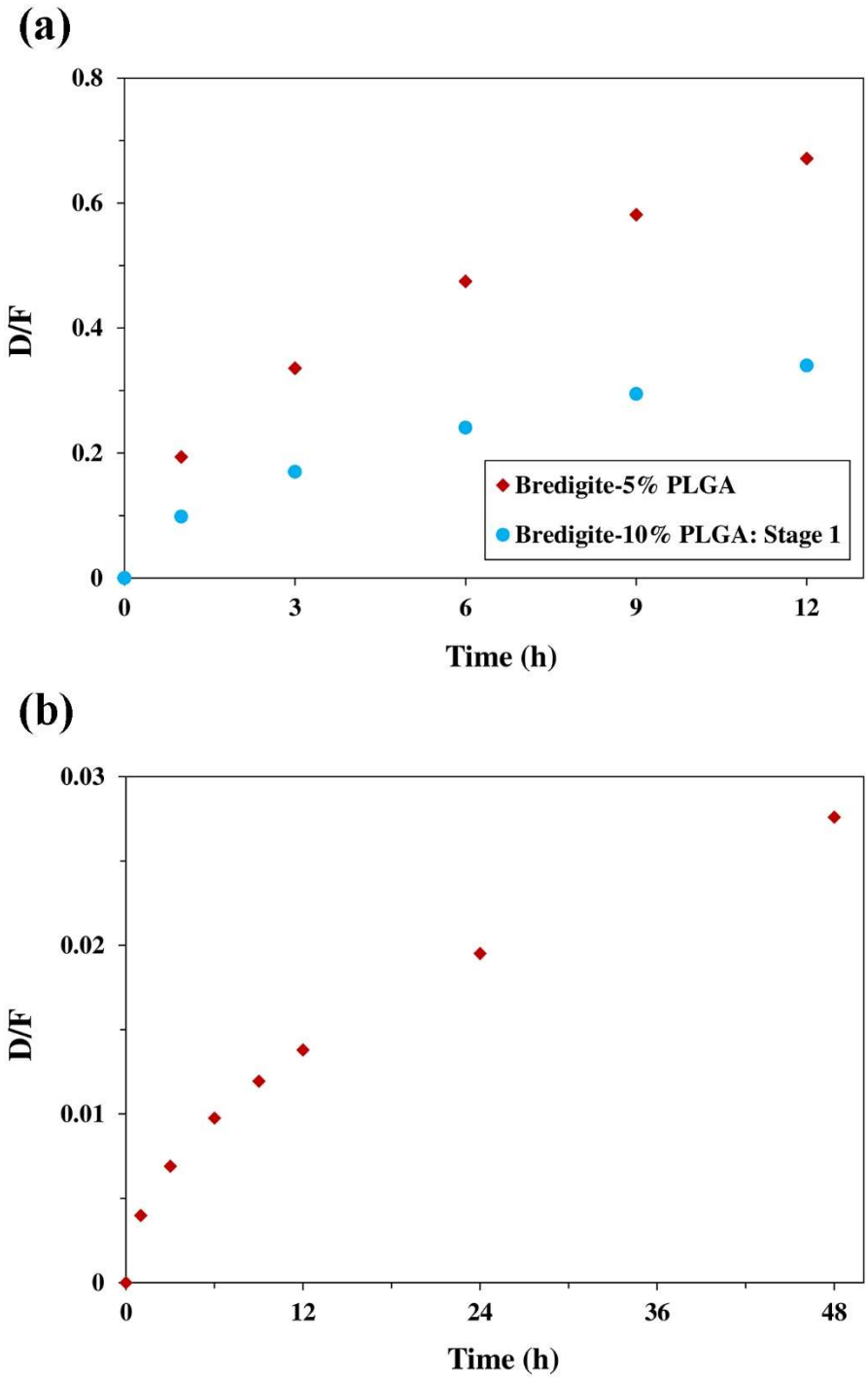

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Fig. 9. Ratio of the dissolution-to-diffusion contributions to the drug release for the 5% and 10% PLGA-coated scaffolds in the 0-12 h range (a) and the 5% PLGA-coated scaffold in the 0-48 h range (b).

By fitting the release data of the 5% PLGA-coated sample with the Peppas-Sahlin equation in the 0-48 h range (Table 5), it can be inferred that the contribution of diffusion is greater than the dissolution mechanism. Accordingly, the *D/F* value (Fig. 9b) is increased from 0.003 to 0.027, indicating the small contribution of the dissolution mechanism for this sample. Compared to the *D/F* values of the 0-12 h range for this sample (Fig. 9a), the 0-48 h range (Fig. 9b) shows the less contribution of dissolution to the overall release. This can be attributed to the fact that during the 0-12 h range, almost all vancomycin molecules adsorbed on partially-coated regions are depleted with a dissolution-controlled mechanism. Thus, their contribution in the 0-12 h range is more pronounced than that in the 0-48 h range, where the Korsmeyer-Peppas fits showed a dominant diffusion-controlled release in the second stage (12-48 h). Since the absolute domination of the dissolution-controlled release mechanism for the bare scaffold is concluded from the Hixson-Crowell and the Korsmeyer-Peppas fits, it is deemed not necessary to further analyze the release data of this sample with the Peppas-Sahlin model.

With respect to the zero-order and first-order kinetics models (Eqs. 9 and 10), only the bare scaffold shows a suitable fit, as presented in Fig. 10 and Table 6. The zero-order model is mainly descriptive of drug carrier systems exhibiting the pure case II transport mechanism (dissolution-controlled). The first-order kinetics is applicable for systems which demonstrate a dependence of release rate on the concentration of the residual drug in the matrix, the behavior which neither of

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the PLGA-coated scaffolds seem to display. The good fit of the bare scaffold with these models reinforces the fact that not only a dissolution-controlled mechanism is dominant for this sample but also the release rate of vancomycin molecules from the bare sample is dependent on the amount of the drug remaining in the matrix.

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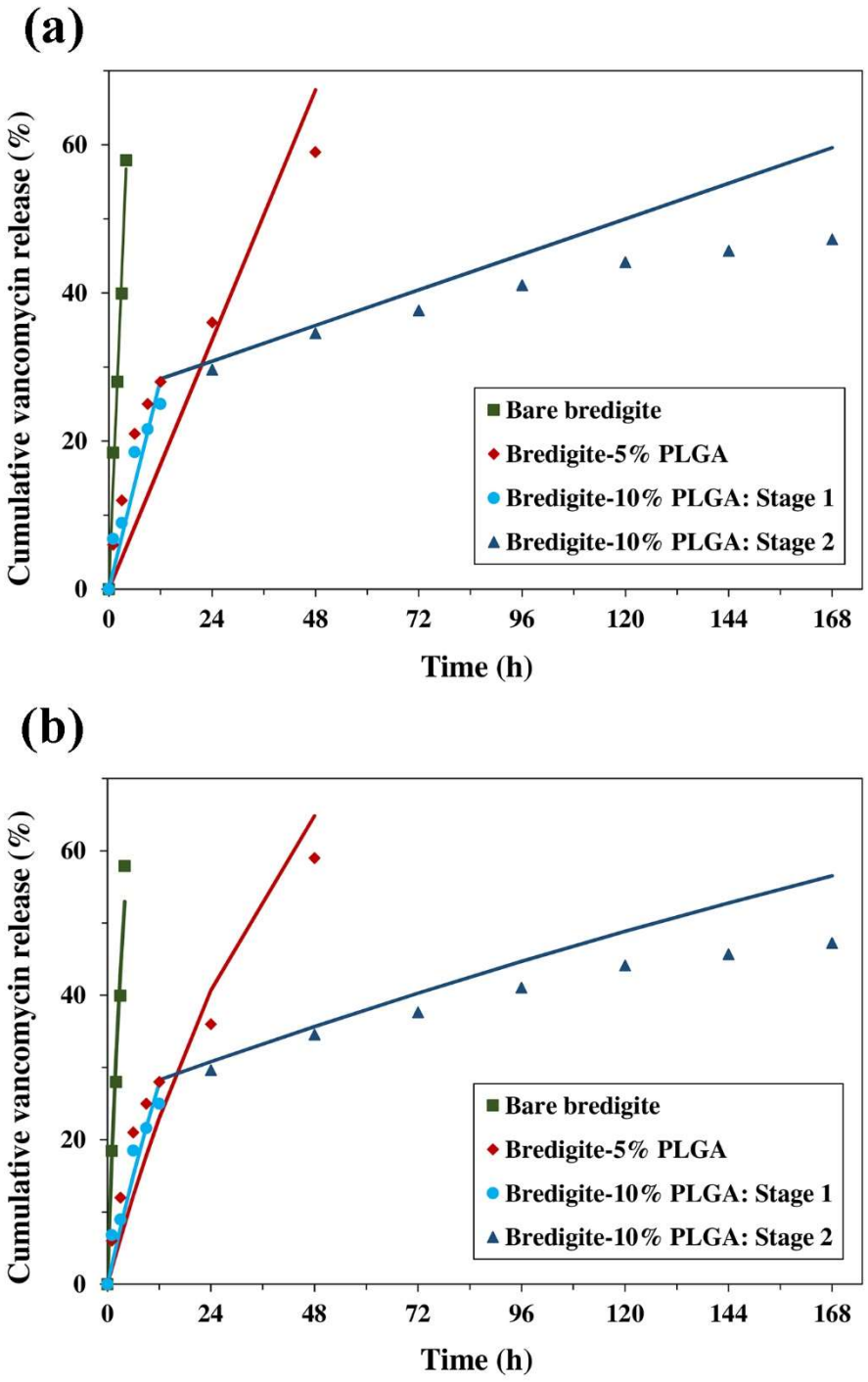

Fig. 10. Fitted zero-order (a) and first-order (b) plots of vancomycin release from the scaffolds.

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Table 6. Correlation coefficients (R_c) of the vancomycin release data fitting with the zero-order and first-order models.

Model	R_c			
	Bare bredigite	Bredigite-5% PLGA	Bredigite-10% PLGA	
			Stage 1	Stage 2
Zero-order	0.97	0.75	0.86	0.82
First-order	0.98	0.88	0.87	0.69

According to the analysis of the drug release data from the scaffolds by using the mathematical models, it is concluded that due to the relatively rapid bioresorption of bredigite [59], the drug release rate of the bare sample is fast and is characterized by a matrix dissolution-controlled mechanism. This was evidenced by the fitting results of the bare scaffold data with the Hixson-Crowell, zero-order and Korsmeyer-Peppas models, whereas other bioceramics like hydroxyapatites and bioglasses possessing slower bioresorption rates tend not to fit well with the dissolution-based models [60]. Accordingly, approaches that hinder the matrix dissolution rate (e.g. polymer coating) can significantly alter the drug release kinetics and mechanism of fast bioresorbable ceramics like bredigite. The good fits of the PLGA-coated samples with the Higuchi, Korsmeyer-Peppas and Weibull models indicates that not only the polymer coatings are successful in limiting the dissolution of the underlying bredigite matrix and in transforming to a diffusion-controlled release mechanism, but also it is possible to further modulate the drug release rate via the adjustment of the PLGA thickness. Additionally, it is understood that the uniformity of the PLGA coating plays a role in determining the overall release mechanism,

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where the partial coverage of the 5%-PLGA coating results in the persisting contribution of the dissolution mechanism, albeit at a significantly lower extent than the bare scaffold. Even, the 10% PLGA-coated scaffold displayed a contribution of the matrix dissolution for a short period of the drug release, signifying the critical role of micro-imperfections in the PLGA layer.

4. Conclusions

In this study, vancomycin impregnated, interconnectedly porous bredigite scaffolds with and without PLGA coating were investigated in terms of the drug release kinetics by using well-established mathematical models. The effect of different thicknesses of the PLGA coating on the release kinetics was also examined. It was found that the inherent, relatively rapid bioresorption of the bare bredigite scaffold leads to a single-stage, fast and dissolution-controlled vancomycin release kinetics. The 5% PLGA coating of the scaffold managed to transform to a slower, single-stage anomalous transport of the drug, where the contribution of diffusion was much more prominent than dissolution. By increasing the PLGA coating thickness in the 10% PLGA-coated sample, the release of vancomycin was further slowed down and displayed a two-stage profile, where its first stage demonstrated a combined action of dissolution and diffusion albeit with the dominant contribution of diffusion. In the second stage, the release was found to be purely diffusion-controlled. Overall, the study demonstrated the versatility of the bredigite scaffolds as matrixes for local drug delivery displaying modifiable drug transport mechanisms that can be tuned to specific therapeutic and dosing strategies with a simple biopolymer coating approach.

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