

Original Research Article

Release profile of oxytetracycline from a bioactive glass/polycaprolactone composite prepared using *Phaeodactylum tricornutum*

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Abstract

Purpose: To evaluate the drug release profile of oxytetracycline (OTC) incorporated into a bioactive glass/polycaprolactone (PCL) scaffold.

Methods: Bioactive glass/polycaprolactone composite was prepared by solvent casting technique at a ratio of bioactive glass: PCL 1:1 and 1:2, and OTC was added at equal concentrations. Drug release and degradability were tested by incubating the samples in simulated body fluid (SBF) for 6 hours and 28 days, respectively. The release profile was evaluated using an ultraviolet (UV) spectrophotometer at a wavelength of 268 nm. Drug incorporation was assessed by using Fourier-transform infrared (FTIR) spectroscopy and scanning electron microscopy (SEM).

Results: The bioactive glass: PCL delivery system developed with a 1:1 combination ratio released 25.58 % OTC after 6 hours in SBF, and with a cumulative weight loss of 15.73 % after 28 days. The bioactive glass: PCL prepared at 1:2 weight % released 18.49 % in 3 hours and displayed a sustained release profile while exhibiting a cumulative weight loss of 8.10 % after 28 days in SBF.

Conclusion: The method reported in this study could be useful for fabricating a scaffold applicable in bone regeneration and having a controlled or sustained drug delivery capability.

Keywords: Bioactive glass, Drug delivery system, Polycaprolactone, *Phaeodactylum tricornutum*

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INTRODUCTION

Antibiotics delivered locally to implanted sites may be used to prevent infections and promote bone repair [1,2]. To sustain the efficacy in a drug-release system associated with bone tissue engineering, the carrier, often referred to as the scaffold, needs to have the right porosity. The drug must also be released under close monitoring over a specified period of time and have a zero kinetic [3,4].

Bioactive ceramics, including hydroxyapatite, calcium phosphate, and bioactive glasses, are currently thought of as drug carriers in novel drug delivery systems in addition to their special qualities as bone tissue scaffolds [5]. These characteristics include bodily fluids' bioactivity, biocompatibility, and biodegradability [5]. Moreover, metallic therapeutic compounds that can biologically interact with a damaged bone

location and treat diseases can be incorporated into a bioactive glass [6].

Polycaprolactone (PCL), a biodegradable aliphatic polyester, is well-known for its desirable properties for biomedical applications, such as its nontoxicity, slow resorption after implantation, and good tensile strength [7]. One crucial characteristic of the materials utilised to create scaffolds for tissue engineering applications is degradation. It is anticipated that in tissue engineering, the rate of material degradation will be comparable to the pace of tissue regeneration. If degradation occurs more slowly than tissue regeneration, it prevents tissue growth; if it occurs faster, the tissue-scaffold connection is broken, which slows the healing process [8].

Several qualities of PCL that make it useful biomaterial in controlled drug delivery include its rubbery texture, adjustable biodegradability, and ease of forming blends, composites, and copolymers. It is a desirable material for use as a supporting device, especially for hard tissue; a good scaffold material for tissue engineering; a desirable material for surgical sutures; and a desirable material for micro and nano drug delivery vesicles [9]. Furthermore, its hydrophilicity and surface roughness can be tailored to give the tissue desirable surfaces and interfacial properties [10,11].

For a controlled drug delivery system to be effective, the drug must be placed onto a biocompatible vehicle to prevent negative effects on bodily systems [12]. In a recent study, silica was extracted from the diatom *Phaeodactylum tricornutum* to prepare a bioactive glass, while the precursor for CaO and P₂O₅ was bovine bone. The extract from the bioactive glass demonstrated a higher degree of cell viability when tested against mouse fibroblast cells [13]. Based on this promising outcome, the work described here is a controlled drug delivery system using bioactive glass that was biologically synthesized and subsequently encapsulated in PCL to determine the release properties of oxytetracycline.

EXPERIMENTAL

Materials

The materials used for this study included bioactive glass derived from *Phaeodactylum tricornutum* (a diatom biosilica) prepared according to a previous report [13], polycaprolactone (PCL), average molecular weight (Mn) 80,000 (Shanghai Macklin

Biochemical Co., Ltd.), chloroform (J.T. Baker), and oxytetracycline (AdvaCare Pharma).

Preparation of bioactive glass/PCL composites

The composites were prepared in two weight ratios of bioactive glass: PCL of 1:1 and 1:2. Initially, the PCL powder was sonicated in chloroform at 45 °C for 5 min to form a solution. Then, the bioactive glass was dispersed in the solution, and the mixture was sonicated for a further 1 hour. The products formed were immediately cast into cylindrical plastic molds and then kept to dry for 5 days in an incubator at 37 °C [14]. The dimensions of the samples after drying were carefully cut to measure 13 mm x 7 mm (diameter x height). The bioactive glass/PCL composite with bioactive glass: polymer with a weight ratio of 1:1 was given the code name 1BG/1P, while the one with bioactive glass: polymer with a weight ratio of 1:2 was code-named 1BG/2P.

Preparation of Bioactive glass/PCL composites loaded with oxytetracycline

To load the oxytetracycline (OTC) drug onto the composites, the steps for the preparation of the bioactive glass/PCL composites were repeated with a similar bioactive glass: polymer weight ratio for both samples. However, after the bioactive glass was dispersed in the polymer solution and the mixture was stirred for 1 hour, 20 wt% of oxytetracycline, initially dissolved in 10 mL chloroform, was added to the mixture, and the mixture was further sonicated for 30 minutes at 45 °C. Afterwards, the samples were cast into cylindrical plastic moulds and allowed to dry for 5 days in an incubator at 37°C. They were further shaped to measure 13 mm x 7 mm in diameter and height, respectively. The bioactive glass/PCL composite with a weight ratio of 1:1 bioactive glass: polymer loaded with the drug was tagged 1BG/1PX, while the one with a weight ratio of 1:2 bioactive glass: polymer with the drug incorporated was code-named 1BG/2PX.

Characterization

The samples were sputter-coated with 5 nm gold and distributed over carbon conductive tape. A scanning electron microscope (SEM; Phenom ProX, 800–07334) running at 30 kV was used to analyse the materials' microstructural properties. With a Fourier Transform Infrared Spectrophotometer (Agilent Technology Cary 630 FTIR) in transmittance mode, the spectra showing the chemical bond properties of the

composites were acquired across the spectral scan range of 4000 – 650 cm^{-1} .

***In vitro* degradation study**

Cylindrical-shaped samples were immersed in 10 mL SBF in clean conical plastic bottles. The SBF was prepared according to standard *in vitro* procedure [15]. Thus, all the containers were initially washed with 1 M HCl, followed by deionized water. Then, under stirring conditions with a magnetic stirrer, each reagent was added gradually to 700 mL of deionised water at 36.5°C in a graduated plastic beaker according to the order shown in Table 1. The 8th and 9th reagents were added slowly to avoid a local rapid increase in pH, which could precipitate apatite. Tris and 1M HCl were used to adjust the pH to 7.40 at 36.5 °C. Finally, the volume of the fluid was made up to 1000 mL in a standard volumetric flask. Thereafter, the samples were incubated at 36.5 °C for 28 days. After incubation, they were washed with distilled water and dried at 37 °C. Degradation was assessed through weight loss estimated using Eq 1 [16], where W_0 represents the initial mass and W_1 is the mass after soaking at a given time in SBF.

$$\text{Weight loss (\%)} = \{(W_0 - W_1)/W_0\}100 \dots\dots (1)$$

Table 1: The order of reagent addition and composition of 1000 mL of the SBF

Order	Reagent	Amount/1000 mL
1	Ultrapure water	-
2	NaCl	7.996 g
3	NaHCO ₃	0.350 g
4	KCl	0.224 g
5	K ₂ HPO ₄ ·3H ₂ O	0.228 g
6	MgCl ₂ ·6H ₂ O	0.305 g
7	1M HCl	39 mL
8	CaCl ₂	0.278 g
9	Na ₂ SO ₄	0.071 g
10	Tris (CH ₂ OH) ₃ CNH ₂	6.057 g

***In vitro* drug release**

The samples loaded with OTC (1BG/1PX and 1BG/2PX) in similar dimensions were used in the *in vitro* drug release study. Three plain and drug-loaded bioactive glass/PCL samples with dimensions 13 mm x 7 mm (diameter x height) were immersed in 10 mL SBF at 37 °C at a pH of 7.4. Drug released into the SBF was evaluated using UV spectrophotometer (Uniscopes SM 7504) at a wavelength of 268 nm. A calibration curve was developed with oxytetracycline concentrations in the range 5 – 40 $\mu\text{g/mL}$. The calibration curve with a linear fitting ($R^2 = 0.998145$) followed Beer's law (Eq 2).

$$A = 0.037 \cdot C \dots\dots\dots (2)$$

where A is the absorbance and C is the concentration of the drug in $\mu\text{g/mL}$.

RESULTS

FTIR spectra of the plain and drug-loaded composites

The FTIR spectrum of the OTC alone (Figure 1) and the composites before and after drug-loading (Figure 2) reveals the successful incorporation of OTC into the composites. The FTIR spectrum of OTC shows major bands around 3443, 2936, 1625, 1431, 1034 cm^{-1} (Figure 1). The intense band at 3477 cm^{-1} is related to the OH stretching vibration in OTC, which is hydrogen-bonded. The small peak around 2936 cm^{-1} is attributed to a C–H stretching vibration [17], whereas the ones near 1625 and 1431 cm^{-1} are attributed to the stretching vibration of C=O and the bending mode of N–H (amide II), respectively [18]. The band at 1034 cm^{-1} is considered the stretching vibration of C–N bond of the amide moiety in OTC [17]. The spectra of the unloaded and drug-loaded composites are presented in Figure 2. The FTIR spectrum of the plain 1BG/1P scaffold (Figure 2 a) shows peaks at 2954, 2866, 1722, 1469, 1420, 1368, 1293, 1237, 805, and 731 cm^{-1} . After OTC loading (1BG/1PX), peaks are seen around 3332, 2933, 1730, 1599, 1498, 1457, 1413, 1320, 805, and 708 cm^{-1} (Figure 2 b). For the plain 1BG/2P sample, peaks were observed at 2948, 2870, 1726, 1532, 1461, 1416, 1368, 1256, 1159, 1029, 957, and 805 cm^{-1} (Figure 2 c). Whereas for the loaded sample (1BG/2PX), peaks emerged at 3355, 2952, 2874, 1726, 1607, 1461, 1416, 1368, 1256, 1159, 1036, 954, 805, and 734 cm^{-1} (Figure 2 d).

Morphological characteristics

The morphology of the samples loaded with OTC and those without is presented in the SEM images (Figure 3) at the same magnification. The plain sample with a lower concentration of PCL (1BG/1P) exhibited a porous microstructure (Figure 3 a). When the sample was loaded with OTC (1BG/1PX), the pores closed up, transforming into a rough, fracture surface with well-distributed particles (Figure 3 b). Figure 3 c shows the SEM image of the plain sample containing twice as much polymer (1BG/2P). The SEM shows a compact surface with no visible open pores. The glass particles are seen as grains encapsulated in the polymer matrix. The surface was more compacted after drug loading (sample 1BG/2PX), as observed in Figure 3 d.

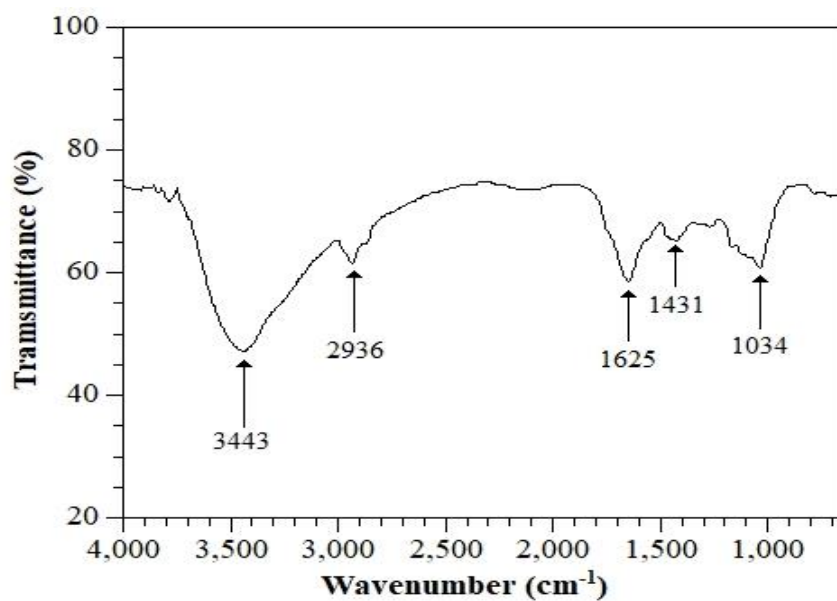


Figure 1: FTIR spectrum of oxytetracycline (OTC)

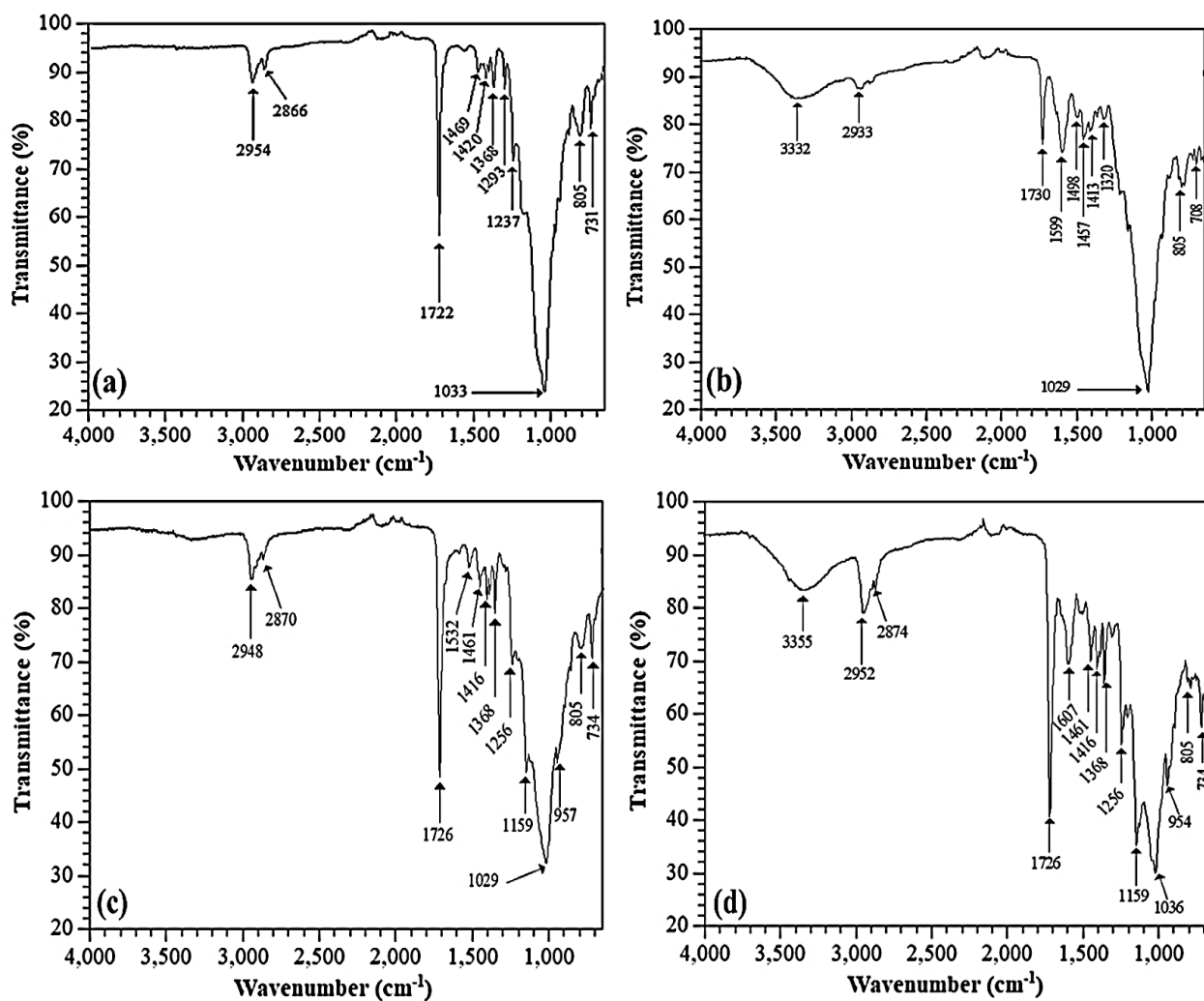


Figure 2: FTIR spectra of (a) 1BG/1P, (b) 1BG/1PX, (c) 1BG/2P, and (d) 1BG/2PX showing the types of bonds present in the composites and the incorporation of OTC

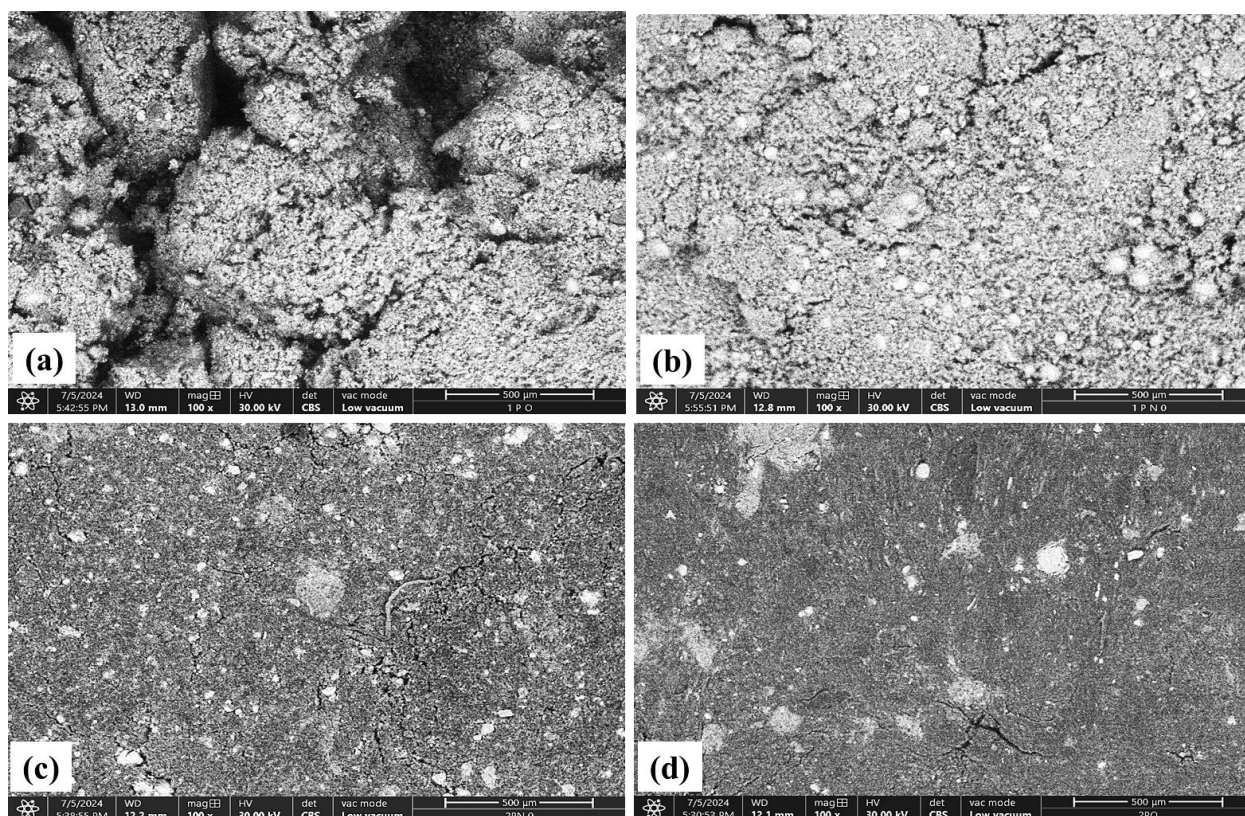


Figure 3: SEM images: (a) 1BG/1P, (b) 1BG/1PX, (c) 1BG/2P, and (d) 1BG/2PX. Scale bar length = 500 μ m

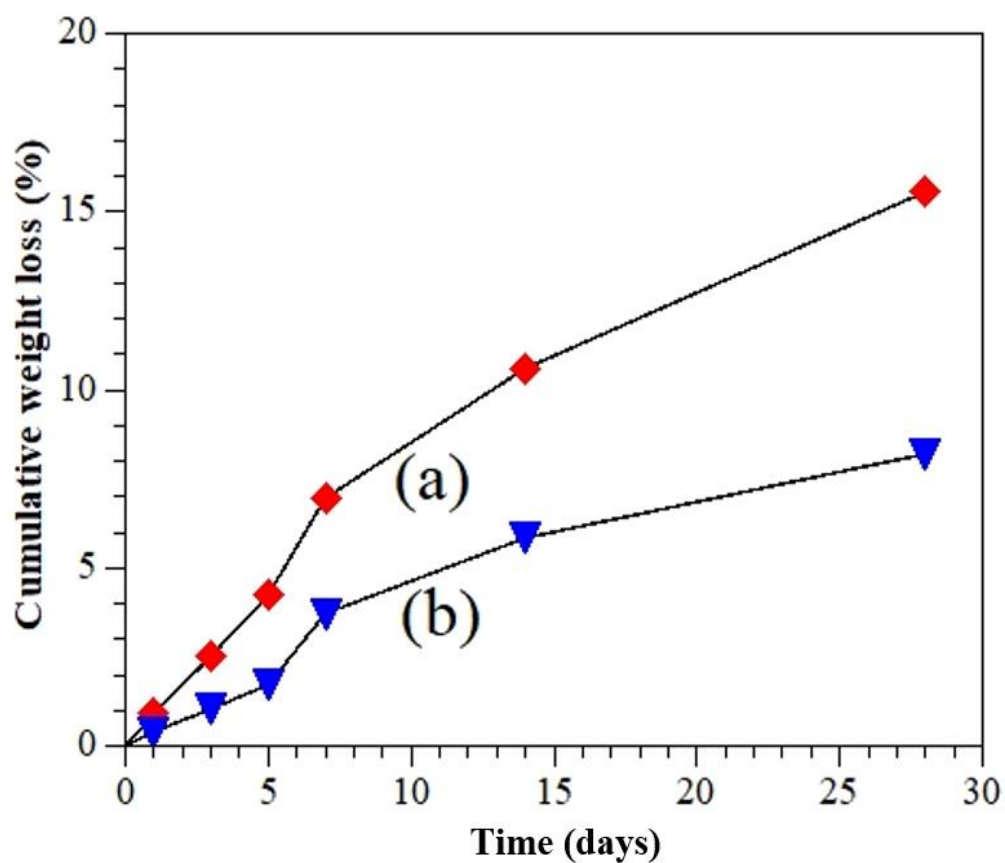


Figure 4: Degradability profile of the drug delivery systems for 28 days for (a) 1BG/1PX, (b) 1BG/2PX

In vitro degradation

Figure 4 reports the degradation of OTC-loaded samples (1BG/1PX and 1BG/2PX) in SBF for 28 days. The composite with a lower PCL concentration (1BG/1PX) exhibited a higher degradation rate (Figure 4 a). At the end of 28 days in SBF, the total weight loss for 1BG/1PX was 15.73 % compared with 1BG/2PX, containing twice the amount of PCL, which was 8.10 %. The amount of weight loss for 1BG/2PX was approximately half that of 1BG/1PX (Figure 4 b).

In vitro drug release

The concentration (in %) of OTC released from composites was standardized against the total amount of OTC incorporated. The results of the cumulative release from the samples in SBF for the first 6 hours are depicted in Figure 5 a and b. The release profile of 1BG/1PX (Figure 5) displays a biphasic pattern. This behaviour is consistent with a drug incorporated into a polymer as an encapsulating material [18]. At 0 - 1 hour, a release of 22.57 $\mu\text{g/mL}$ was detected, which corresponded to 15.03 % of the total concentration of the encapsulated drug. This initial stage, called burst release, is attributed to the dissolution of the drug present on the surface of the sample in the SBF [14]. This stage is maintained for 2 hours as the cumulative release reached 33.14 $\mu\text{g/mL}$, indicating 22.06 % cumulative drug release. The second stage began after 3 hours, where 33.57 $\mu\text{g/mL}$ of the drug was released, indicating 23.68%. Then, after 4, 5, and 6 hours, 36.60 $\mu\text{g/mL}$ (24.37%), 7.357 $\mu\text{g/mL}$ (24.87%), and 38.492 $\mu\text{g/mL}$

(25.58%) of the drug, respectively, were released.

Figure 5 b shows the release profile of 1BG/2PX in SBF at pH 7.4 and 37 °C. The OTC cumulative release also presented a biphasic pattern. At 0 - 1 hour, a release of 18.58 $\mu\text{g/mL}$ was detected, corresponding to 12.37 % of the total concentration of the encapsulated drug. The cumulative release after 2 hours was 26.39 $\mu\text{g/mL}$, indicating 17.59 %. From 3rd to 6th hours, the total cumulative amount recorded was 22.76 $\mu\text{g/mL}$ (15.17%). The release rate slowed after 3 hours, typical of a sustained-release system [19]. Altogether, the release rate of 1BG/2PX was lower than that of 1BG/1PX.

DISCUSSION

The incorporation of OTC into composite delivery systems and the presence of PCL and bioactive were established by investigating the bonds in the composites and their morphological features using FTIR and SEM, respectively, before and after it was loaded with the drug. Before the drug was added to the composite, the peaks associated with PCL were observed at 2954 and 2866 cm^{-1} , which were attributed to the characteristic CH_2 asymmetric and symmetric vibrations, respectively. The sharp peak at 1722 cm^{-1} was due to the stretching vibration of $\text{C}=\text{O}$ [20]. The peaks around 1469 – 1368 cm^{-1} were related to CH_2 bending vibration, whereas the peaks at 1293 and 1237 cm^{-1} are considered for the asymmetric and symmetric stretching modes of $\text{C}-\text{C}$ bond [21] in PCL.

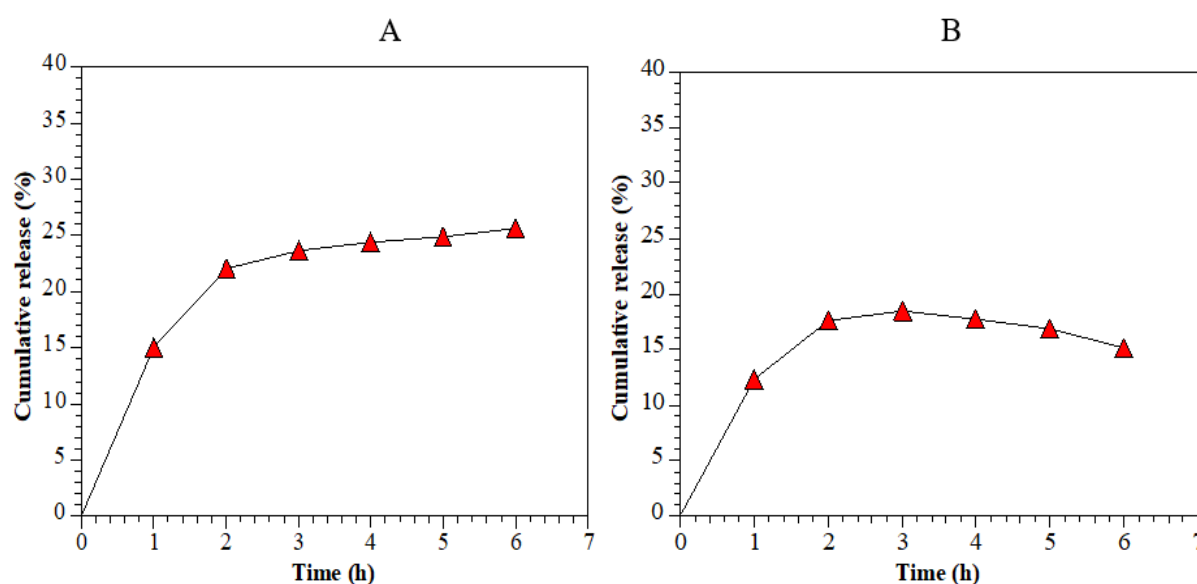


Figure 5: Drug release profiles in SBF for the first 6 hours. (A) 1BG/1PX, (B) 1BG/2PX

The presence of bioactive glass in the composite was identified from the peaks at 1033, 805, and 731 cm^{-1} . The intense peak near 1033 cm^{-1} represents the asymmetric vibrational stretching signal of the Si-O-Si bond, while its symmetric stretching mode is observed around 805 cm^{-1} [20]. The signal for the vibrational stretching of the SiO_4^{4-} tetrahedron in the silicate is observed near 731 cm^{-1} [20].

In the FTIR spectrum of the plain sample 1BG/2P, there was a close similarity in the vibrational modes to 1BG/1P, although there were minor shifts in vibrational frequencies. Slight enhancement in peak intensities was also observed, which might be related to the increase in the concentration of PCL in 1BG/2P relative to 1BG/1P. All the peaks related to CH_2 , $\text{C}=\text{O}$, and $\text{C}-\text{C}$ bonds in the PCL were also prominent in the spectrum, along with those identified for the silicate bioactive glass.

Evidence of drug incorporation onto the OTC-loaded samples (1BG/1PX and 1BG/2PX) was confirmed by examining the FTIR spectra of 1BG/1PX and 1BG/2PX, respectively. As observed, apart from the spectrum of 1BG/1PX retaining all the peaks associated with the constituents in the composite, peaks related to OTC are seen at 3332 and 1599 cm^{-1} , representing the stretching vibration of OH and $\text{C}=\text{C}$ of the benzene ring in the drug. For 1BG/2PX, the vibrational frequencies of OH and $\text{C}=\text{C}$ are located at 3355 and 1607 cm^{-1} , respectively.

When the OTC was added, the surface morphology became even more compact, appearing smoother and with a visible reduction in surface roughness. This indicates that the glass particles and the drug were strongly embedded in the PCL matrix. The various morphological characteristics could influence the drug release, bioactivity, cells, and protein attachment when applied as a scaffold in repair and drug delivery. The two samples, 1BG/1PX and 1BG/2PX, presented different modes of release and degradability, which depended on the quantity of PCL added. 1BG/1PX release profile displayed a zero-order kinetic, which signals a controlled delivery of the drug. This property is beneficial for maintaining a drug concentration within the therapeutic window over an extended period [12].

The 1BG/2PX sample exhibited a sustained release profile. It was evident that when the concentration of PCL doubled, the release of OTC became slower. Multiple factors control the rate of diffusion of a drug. Solubility of the drug in

the dissolution medium, polymer matrix's micro-environment, and thickness of the diffusion layer are some examples [22]. Furthermore, an increase in the rate of polymer matrix erosion leads to increased drug release. Thus, in the case of 1BG/2PX, the polymer matrix erosion was low in SBF as the PCL concentration was doubled, giving rise to a thick diffusion layer. This ultimately slowed the release. This implies that a delivery system can be tailored to obtain a slower release rate by adjusting the polymer content and, therefore, achieve a prolonged therapeutic effect over a lengthy period. Also worthy of note was the difference in the rate of degradability of 1BG/1PX and 1BG/2PX, which was also related to the influence of PCL concentration. Accordingly, the degradation rate of 1BG/1PX was higher than that of 1BG/2PX.

The morphological characteristics of 1BG/1PX and 1BG/2PX support the differences in their release and degradation rates. 1BG/2PX displayed a more compact surface due to a higher concentration of PCL, which provided more sites to enable the stronger encapsulation and bonding of the drug with the polymer matrix compared with 1BG/1PX, containing half the concentration of PCL. Some authors have stated that an increase in polymer concentration leads to a denser, more rigid scaffold structure that decreases the rate of solution penetration [23,24]. This assertion is also supported by the morphology of the samples, which showed that 1BG/2PX presented a more compact architecture relative to 1BG/1PX.

CONCLUSION

A release system composed of a bioactive glass and polycaprolactone polymer has been developed. The silica component of the bioactive glass was derived from the diatom, *Phaeodactylum tricornutum*, as a green precursor. Sustained release has been obtained for the composite prepared with twice the amount of PCL. This outcome could be a useful strategy in bone tissue engineering, where a construct is designed to possess an intrinsic bone regenerative capacity and a controlled or sustained release ability of an antibiotic for the treatment of an infected bone repair site.

DECLARATIONS

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Conflict of Interest

No conflict of interest is associated with this work

Contribution of authors

We declare that this work was carried out by the author(s) named in this article, and all liabilities relating to claims to the content of this article will be borne by the authors. Enobong R. Essien: Conceptualization, methodology and writing original draft. Oludare F. Tolulope: Validation. Cordelia U. Dueke-Eze: Investigation. Violette N. Atasie: Project administration. Ngozi A. Adeleye and Rahmot D. Adewole: Data analysis

Ethical approval

Not applicable

Availability of data and materials

The data supporting the research findings are available from the corresponding author upon reasonable request.

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