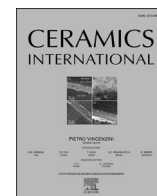




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Corrosion resistance, in vitro cell attachment and drug release of heterostructured CaTiO_3 films on titanium

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ABSTRACT

Calcium titanate (CaTiO_3), a perovskite-type oxide, has garnered significant attention in recent years due to its unique structural characteristics, high chemical stability, strong catalytic activity, non-toxic nature, and ease of synthesis. Here, we investigate the crucial aspects related to the morphology and properties of CaTiO_3 (CTO) film obtained by the hydrothermal method from titanium dioxide (TiO_2) nanotube template and $\text{Ca}(\text{OH})_2$ precursor for biomedical applications. Following the discussion of CaTiO_3 film characterization, the advantages of CaTiO_3 film will be introduced, such as their high surface area controlled by the morphological parameters, which provides better adsorption of bioactive molecules. The corrosion properties resistance of CTO film were evaluated and demonstrated to be significantly enhanced compared to the original Ti substrate. We further discuss in vitro cellular compatibility on the CTO film. In addition, the unique properties and structure of the tested CTO film contribute to its ability to slow drugs releasing. The present investigate also overviews the current state of heterostructure, surface properties, corrosion resistance, biocompatibility and drug delivery applications of CaTiO_3 film on Ti for biomedical applications.

1. Introduction

The challenges associated with bone implants have attracted significant attention from both medical practitioners and materials researchers. Various factors, such as material compatibility, tissue regeneration capability, and the risk of post-implantation infection, can significantly impact the success of orthopedic implants. Inflammation and bacterial infection represent the most critical complications in orthopedic surgeries [1,2]. Therefore, after surgery, patients often require a significant amount of medication to reduce the risk of infection, which can adversely affect the implant site. How medication can effectively prevent post-implantation infection has been a long-standing question. Oral and intravenous drug administration are the most prevalent methods employed today. Systemic drug administration cannot be

considered a proper solution to eliminating these problems as a result of some restrictions, such as low drug solubility, poor distribution [3], uncontrolled pharmacokinetics [1,2], poor targeting and serious side effects in non-target tissues [4,5]. Therefore, new drug delivery systems are required to release drugs at a specific rate and dosage in the target tissues [6]. Local drug delivery has several advantages over conventional drug delivery systems including lower required dosage, lower probability of promoting antibiotic resistance, extended-release time, the possibility of combining systemic and local drugs with different kinetics.

Nanotechnology has enabled the fabrication of various nanostructures with unique properties for biomedical applications. Among these, titanium dioxide (TiO_2) has gained significant attention. TiO_2 nanotubes offers a wide range of potential applications due to its

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nanoscale features, low toxicity, excellent biocompatibility, intrinsic properties, and versatile fabrication techniques [7–9]. TiO₂ nanotubes exist mostly as rutile and anatase phases which both of them have tetragonal structures. However, rutile is a high-temperature stable phase and has an optical energy band gap of 3.0 eV (415 nm), anatase is formed at a lower temperature with an optical energy band gap of 3.2 eV (380 nm) and refractive index of 2.3 [10]. TiO₂ has been the subject of extensive research for biomedical applications, particularly in the fields of implantation and drug delivery [4,11,12]. However, to enhance its suitability for biomedical implants, it is necessary to find a material with appropriate components essential for bone, such as calcium, magnesium, and zinc. These elements contribute to improved biocompatibility and osseointegration.

CaTiO₃, a well-known bioceramic, has increasingly drawn attention from researchers. As a multifunctional material, it possesses significant properties such as optical [13], high dielectric constant [14], ferroelectric [15], chemical stability [16], low dielectric loss [17], cost-effectiveness [18], and environmentally friendly characteristics [19]. Various wet chemical methods have been employed to synthesize CaTiO₃ and achieve the desired properties. These methods include sol-gel [20], co-precipitation [21], the combustion method [22], and the hydrothermal method [23]. Among these techniques, we opted for the hydrothermal method due to its advantageous ease of fabrication. Moreover, CaTiO₃ offers other advantages such as low cost, easy synthesis, and high stability, along with corrosion resistance. The CaTiO₃ possesses distinctive physical and chemical properties, making it an appealing choice for applications in the field of biomedical science and healthcare [24,25]. With a calcium composition closely resembling that of bone, this material exhibits excellent biocompatibility and is well-suited for bone implants and regeneration applications [26]. Additionally, it can be integrated into implants structures to provide mechanical support and encourage bonding with bone. However, to the best of our knowledge, there is no report on heterostructure of CaTiO₃ film on titanium for corrosion, biocompatibility and slow drugs releasing for health care applications. Therefore, the aim of the present study was to synthesize CaTiO₃ film on Ti substrate using TiO₂ nanotubes template and Ca(OH)₂ precursor through hydrothermal reaction at 200 °C for 24 h. The results of this study will open a new horizon to the next generation of structure and surface modification, slow drugs releasing with a controlled biocompatibility. The synthesis of CaTiO₃ film could be a suitable materials in dental and orthopedic implants to avoid any infections after surgery with desired and sustained drug releasing. The impact of the CaTiO₃ film on cell compatibility was also assessed through in vitro cell culture.

Curcumin is a bright yellow compound produced by plants of the *Curcuma longa* species. It is the principal curcuminoid of turmeric (*Curcuma longa*), a member of the ginger family, Zingiberaceae. It is sold as a herbal supplement, cosmetics ingredient, food flavoring, and food coloring [27]. According to Indian traditional medicine, curcumin is known for its bone-healing properties. Its administration for the healing of fractures and increasing bone density is well documented in earlier reports [28].

In this study, we have successfully synthesis of CTO film on the titanium substrate for potential application in biomedical implants with controlled slow drugs releasing. The heterostructured structure of CTO film makes it an ideal candidate for sustained slow drugs releasing. Additionally, the CTO film exhibits excellent properties such as hydrophilicity, surface roughness, and corrosion resistance. The CTO film demonstrates good biocompatibility as evidenced by cell attachment and the formation of a mineralized layer on the CTO films. The sustained release of curcumin over a 14 days period further supports the potential of CTO film for both biocompatibility and slow drugs release applications.

2. Experimental

2.1. Synthesis of TiO₂ nanotubes

The commercial titanium plates (10 × 10 × 1 mm³, Merck, 99.9%) were used for substrates. The Ti plates were first washed ultrasonically with acetone for about 20 min, then completely washed with distilled water, and finally dried in a vacuum oven at 40 °C for 2 h. Ti plates are used as Ti electrodes after completely washing. The electrolytes of the anodizing method were prepared using ammonium fluoride (NH₄F, Sigma, 99.9%), ethylene glycol solution (C₂H₆O₂, Sigma, 99.9%), and H₂O. The anodizing process was carried out at 50 voltages for 1 h using a DC power supply [29,30].

2.2. Synthesis of CaTiO₃ films

CaTiO₃ film was synthesized using a hydrothermal process on the TiO₂ nanotube template. The TiO₂ nanotube template was anodized on a Ti substrate plate. The starting materials for the synthesis of CaTiO₃ film were TiO₂ nanotube template, calcium hydroxide Ca(OH)₂ (99.9% purity, Merck) and sodium hydroxide NaOH (≥97.0% purity, Merck) were used as precursor. Initially, 0.4 g, 0.5 g, and 0.6 g of Ca(OH)₂ were separately dispersed in 40 mL of deionized water under continuous stirring. Separately, 3.2 g of NaOH was dissolved in 10 mL H₂O. These two solutions were then mixed together, yielding a total volume of 50 mL. Therefore, the precise concentrations of Ca²⁺ in the final reactions are 0.108 M, 0.135 M and 0.162 M, respectively, while the NaOH concentration was maintained at a reasonable level of 1.6 M. The resulting mixture was sealed in a 100 mL Teflon-lined stainless steel autoclave containing the TiO₂ nanotube template and then heated at 200 °C for 24 h. After the hydrothermal process, the samples were collected, washed with deionized water (three times) and absolute ethanol (two times), and dried at 60 °C for 12 h.

2.3. Surface characterization

The crystal structure and morphology of the obtained samples were characterized using an X-ray powder diffractometer (Siemens D500, using Cu-K_α radiation at $\lambda = 1.5406 \text{ \AA}$; tube voltage = 40 kV; tube current = 40 mA). Field emission scanning electron microscopy (FE-SEM, JEOL JSM-7600F) was employed to investigate the morphology of CaTiO₃ film. FE-SEM equipped with EDS (Gatan, UK) was used for the elemental analysis of the samples. A 3D optical profilometer and surface roughness measurements of the materials were performed using digital optical microscope (VHX -7000). The superhydrophilicity property was assessed by determining the contact angle between a water droplet and the underlying surface. The surface chemistry was characterized by Nexsa XPS System.

2.4. Corrosion resistance measurement

The corrosion resistance properties of the Ti substrate and CTO film were evaluated through Tafel plot measurements conducted in simulated body fluid (SBF) with a neutral pH of approximately 7. These measurements were performed at a controlled temperature of 25 °C to simulate physiological conditions. The experimental setup included the test sample as the working electrode, a platinum electrode as the counter electrode, and a saturated calomel electrode (SCE) as the reference electrode, all immersed in the SBF solution.

Tafel plots were recorded within a potential range of −100 mV to 100 mV at a scan rate of 10 mV/s to obtain electrochemical parameters such as corrosion resistance (R_p), corrosion current density (I_{corr}), and corrosion potential (E_{corr}). These parameters provided insights into the comparative corrosion performance of Ti substrate, TiO₂ nanotube, and CTO film.

The analysis was conducted using an AutoLab PGSTAT302N system

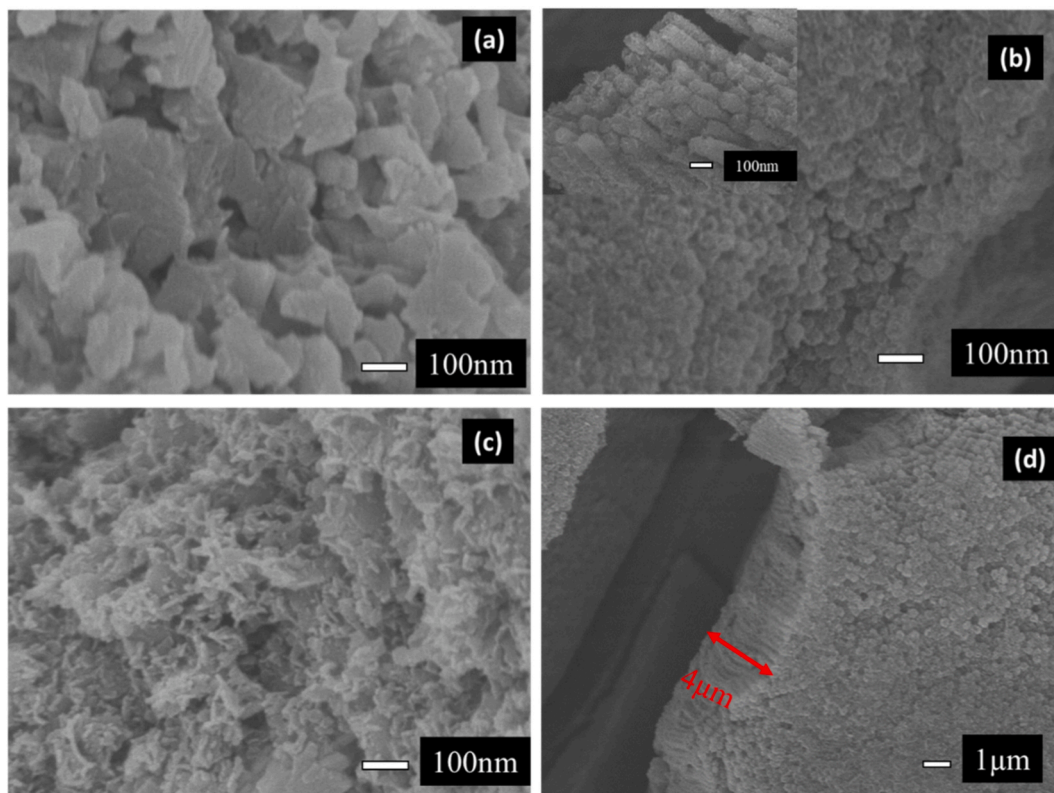


Fig. 1. FESEM of CTO with different Ca^{2+} content: (a) 0.108 M, (b) 0.135 M, (c) 0.162 M, (d) Cross-sectional image of the CTO with Ca^{2+} content of 0.135 M.

integrated with Nova 2.1.7 software to ensure precision and reliability in data acquisition. This approach facilitated the assessment of the coatings' ability to enhance corrosion resistance under simulated physiological conditions.

2.5. In vitro drugs releasing

The in vitro drug release characteristics of the curcumin-loaded CTO film were investigated in a phosphate buffered saline (PBS) solution at pH 7.4. To maintain proper sink conditions for the hydrophobic curcumin throughout the study, a bulk release medium was first prepared by

incorporating 25 μL of Tween 80 into 50 mL of PBS, yielding a final surfactant concentration of 0.05% v/v. Subsequently, the curcumin-loaded CTO film and the bare Ti substrate (flat, polished, and cleaned titanium) were immersed separately in vials containing 5 mL of prepared PBS/Tween 80 solution. At predetermined time intervals, a 3 mL aliquot of the release medium was withdrawn from each vial for absorbance analysis. To maintain a constant volume, 3 mL of fresh, pre-warmed PBS/Tween 80 solution (0.05% v/v) was immediately replenished back into the respective vials. Absorbance measurements were performed every 1 h during 6 h, followed by measurement every 24 h until the entire drug amount was released into the PBS. Absorbance was

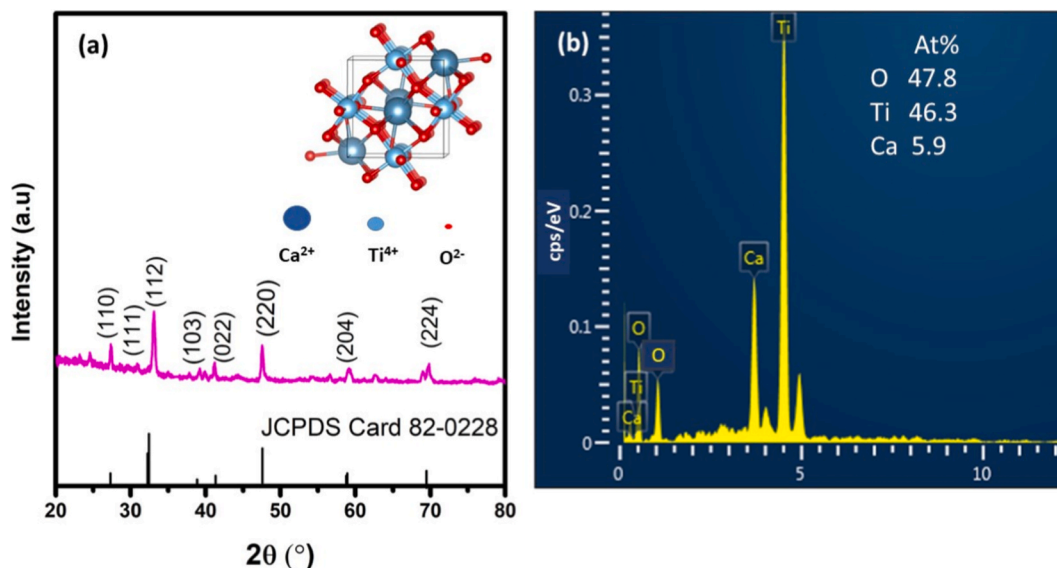


Fig. 2. (a) XRD of CTO film, (b) EDS of CTO film.

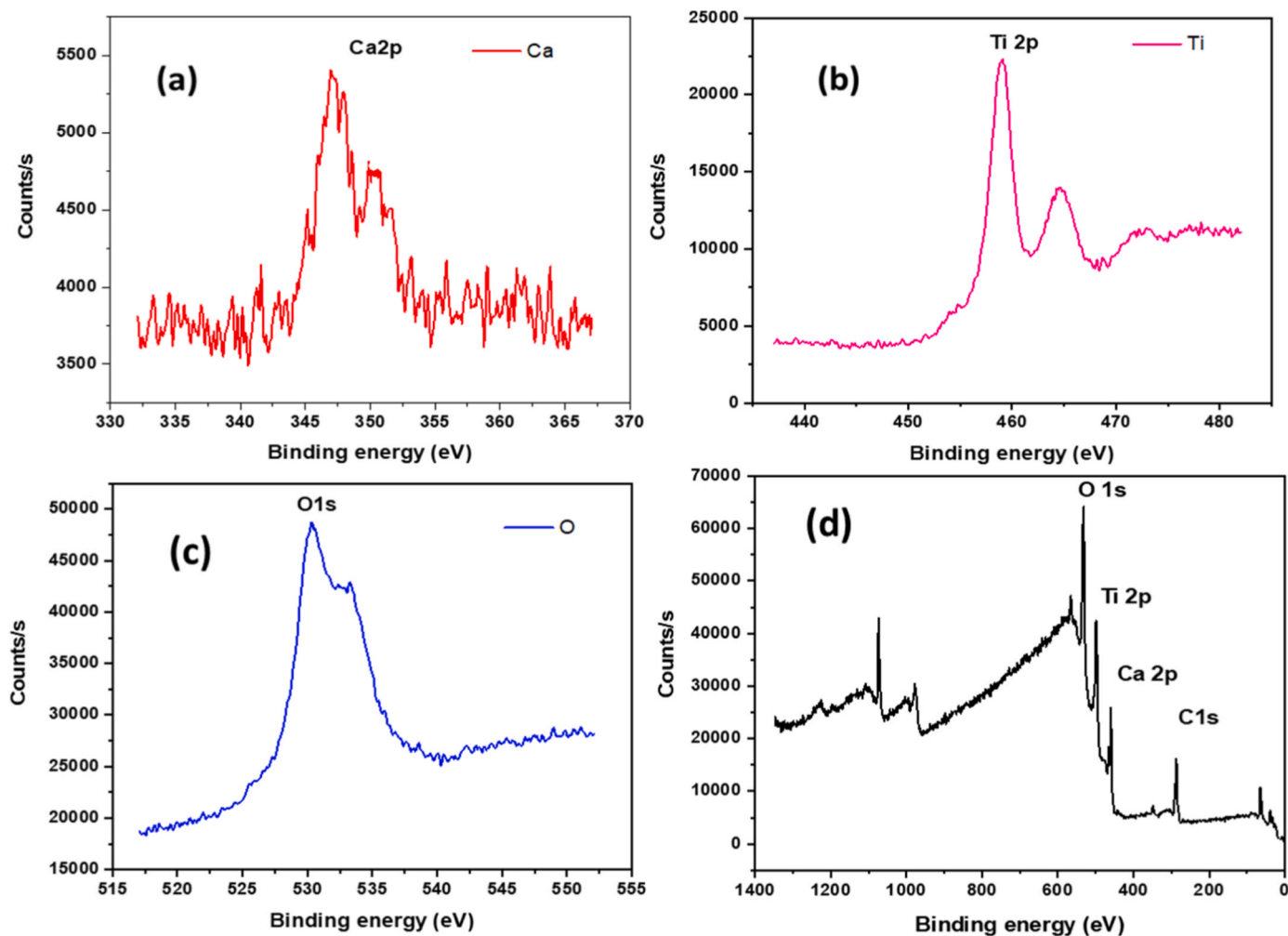


Fig. 3. XPS of CTO film. (a) spectra of Ca 2p, (b) spectra of Ti 2p, (c) spectra of O 1s, (d) the survey of CTO film.

recorded using an ELISA and the released curcumin was measured by plotting against a curcumin standard curve. The released curcumin was expressed as a percent of curcumin. The reported values are expressions of the meaning of three independent runs.

2.6. Cell culture

The CTO film were put into 24 multi-well plates for cell seeding to assess the biocompatibility of the materials. Mouse kidney cell line (BHK-21, ATTC, CCL-10) were suspended at a density of 2.3×10^4 cells/ml in Dulbecco's Modified Eagle Medium (DMEM). Subsequently, 1 mL of the cell suspension was added to each well containing the materials and then placed under standard cell culture conditions (i.e., 37 °C in a 5% CO₂ environment) for 2 and 3 days. The cell culture medium was changed every 2 days. In this study, pure Ti substrate, sized $10 \times 10 \times 1$ mm³, were used as controls. In the cell observation, cells were washed multiple times with PBS and fixed with paraformaldehyde. The cells were further incubated with fluorescent phalloidin 555 (Invitrogen) in 45 min for stain actin cytoskeleton and DAPI (Himedia) in 10 min for nuclear labelling. Cells were washed repeatedly with PBS after each staining. Cell morphology was visualized under confocal laser scanning microscope (FV3000RS, Olympus).

3. Results and discussion

3.1. The surface morphology and structure of CaTiO₃ films

Fig. 1 shows the morphology of CTO film synthesized with different Ca²⁺ contents. The CTO film display a cubic structure morphology as the films synthesized by the Ca²⁺ content of 0.108 M, Fig. 1a. Interestingly, the CTO film synthesized with a Ca²⁺ content of 0.135 M exhibits a nanotube structure which is due to the originating from TiO₂ nanotube template. In particular, the inset of Fig. 1b observed that the nanotubes have the heterostructured structure with diameter about 60–80 nm which is considered one of the unique and ideal architectures for biomedical applications. In addition, the cross-section of CTO film with the Ca²⁺ content of 0.135 M displayed the thickness of 4 μm, Fig. 1d. As the Ca²⁺ content increase to 0.162 M, the nanotube structure of CTO film still observed but it's structure is inhomogeneous morphology, Fig. 1c. Therefore, the Ca²⁺ content of 0.135 M was chosen for the next experiments.

Fig. 2a shows the XRD pattern of CaTiO₃ film synthesized with the Ca content of 0.135 M. The presence of the CaTiO₃ phase was confirmed by comparing the XRD patterns of the CaTiO₃ film with the corresponding inorganic crystal structure database (ICSD) entry number 06-2149. All diffraction peaks were assigned to the cubic structure of the CaTiO₃ film with the Pm $\bar{3}$ m space group. Energy dispersive X-ray spectroscopy (EDS) analysis, as presented in Fig. 2b, was employed to provide additional evidence of the successful synthesis of CTO film. The results indicated that the synthesized material consists of elements such as

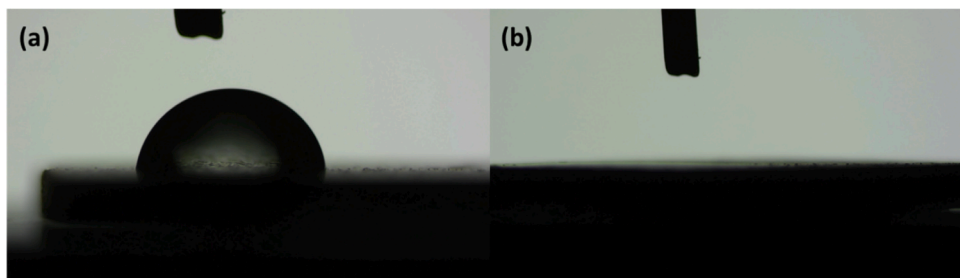


Fig. 4. Contact angle of (a) Ti substrate and (b) CTO film.

calcium, titanium, and oxygen, and no other elemental components were detected.

Fig. 3 presents the XPS spectra of CTO film, confirming the chemical states of the elements within the sample. The Ca 2p spectrum (Fig. 3a) exhibits two characteristic peaks located at approximately 347–348 eV and 351–352 eV. These are assigned to the Ca 2p_{3/2} and Ca 2p_{1/2} transitions of Ca²⁺, respectively. As shown in Fig. 3b, the Ti 2p spectrum displays two prominent peaks centered at 458.5 eV and 464.2 eV, corresponding to Ti 2p_{3/2} and Ti 2p_{1/2} of the Ti⁴⁺ state. The spin-orbit splitting of approximately 5.7 eV further confirms the presence of titanium in its tetravalent state. The O 1s peak (Fig. 3c) located at 530 eV is attributed to lattice oxygen (O²⁻) within the oxide structure. Conversely, a weak shoulder at higher binding energies may originate from surface hydroxyl groups or adsorbed oxygen species [31]. These findings demonstrate that the elements exist in their expected oxidation states, confirming the formation of a stable oxide network.

Fig. 3d illustrates the XPS survey spectrum of CaTiO₃, identifying the primary surface elements as Ti, O, and Ca. Consistent with the EDS results, the survey spectrum confirms that the elemental composition of the CaTiO₃ surface consists predominantly of calcium, titanium, and oxygen. The C 1s peak observed at 285.5 eV, corresponding to adventitious carbon, was utilized as a reference to calibrate the binding energy positions for all identified elements.

3.2. Bioactivity

3.2.1. Water contact angle measurement

Wettability is one of the important characterization of biomedical implant, due to its ability to accelerate cell adhesion and spreading cell

processes, thus, achieving shorter healing periods [32]. Many methodologies have been proposed to functionalize implant surfaces with a high degree of hydrophilicity [33,34]. Moreover, the water-soluble drug loading efficiency also improves in the high wettability surfaces. Therefore, contact angle measurement, the primary way to investigate the degree of affinity between water and surfaces, becomes vital to characterizing the surfaces of drugs releasing implants. Even though wetting has been recognized as an important surface property of implants, published data are very sparse. Generally, wettability is quantified by the angle between the tangent line to a liquid drop's surface at the three-phase boundary and the horizontal solid's surface. In principle, the water contact angle measurement can range from 0° to 180°. Surfaces with water contact angle measurement lower than 90° are designated as hydrophilic, and those with water contact angle measurements very close to 0 are super hydrophilic. Surfaces with water contact angle measurement above 90° are considered hydrophobic, and those with water contact angle measurement above 150° are termed super-hydrophobic. Here, the wettability of samples (Ti substrate, and CaTiO₃ film) was studied. The contact angles of Ti substrate, and CaTiO₃ film were 71.9°, and 0°, respectively (Fig. 4). The CTO film in Fig. 4b exhibits superior wettability, demonstrating the highly hydrophilic property of the CTO film. This remarkable property is attributed to the unique heterostructured structure of the CTO films, which significantly enhances its water absorption capacity. The micro-pores structure provides the channels for the penetration and absorption of water molecules.

3.2.2. Surface characteristics of materials

Roughness has been reported to directly influence the rate of healing and cell adhesion and proliferation [34,35]. When a surface has

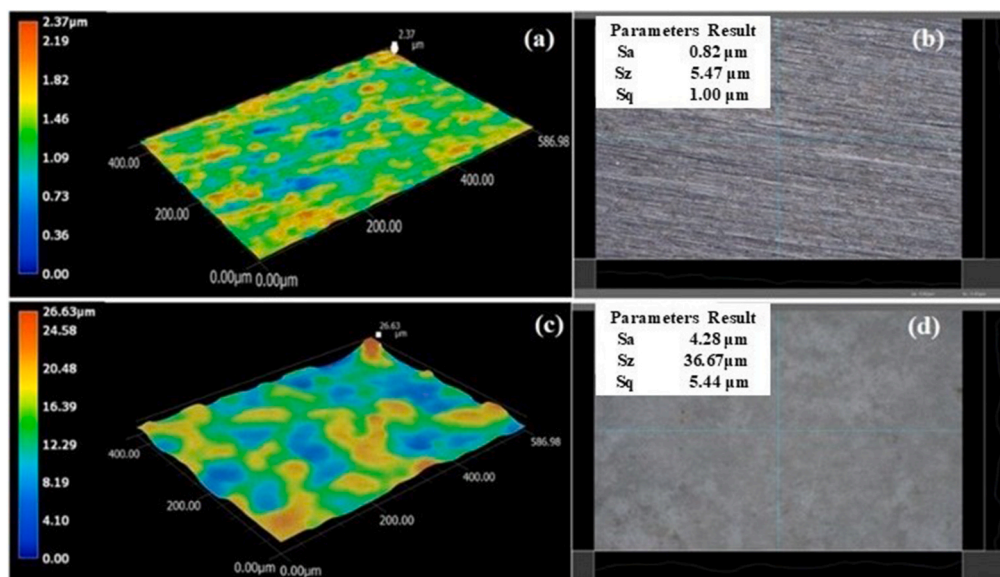


Fig. 5. VHX of the materials; (a, b) Surface roughness and morphology of Ti substrate, (c, d) Surface roughness and morphology of CTO film.

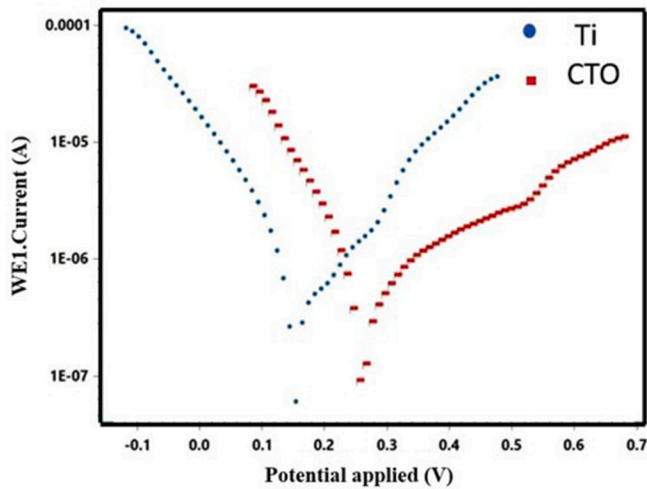


Fig. 6. The Tafel curves of the Ti substrate and the CTO film.

irregular characteristics, cells infiltrate and compact themselves in the surface roughness, generating greater intercellular contact, which is of paramount importance for nutrition and cell evolution [36]. It has been well-established that surface topography significantly influences cell culture and material performance [37,38]. To investigate this further, we utilized digital VHX microscopy to characterize surface roughness. In particular, we focused on the parameter S_a (arithmetic mean height), which quantifies the average deviation of the surface profile from the mean line. Fig. 5 clearly demonstrates a substantial difference in surface roughness between Ti substrate and CTO film. Surface roughness of CTO film was $4.28 \mu\text{m}$, whereas the Ti substrate exhibiting a roughness value of $0.82 \mu\text{m}$, which is 5.2 times higher than that of the Ti substrate. This significant enhancement in the surface roughness of CTO film is expected to promote cell growth effectively.

3.2.3. Corrosion resistance of the CTO film

The corrosion resistance properties of materials are an indispensable factor for materials intended for biomedical implants. Specifically, Fig. 6 and Table 1 clearly present the corrosion characteristics of CTO film compared to Ti substrate.

The results demonstrate a significant improvement in the corrosion resistance of the CTO film compared to bare Ti substrate (Table 1). The corrosion potential (E_{corr}) of the treated samples increased considerably, with CTO film showing enhancements of 67.72%, compared to the bare Ti substrate. This indicates that the coatings form a passive layer that protects the Ti metal surface, reducing its susceptibility to corrosion in simulated body fluid (SBF). Meanwhile, the corrosion current density (i_{corr}) decreased significantly in the CTO film ($6.3201 \times 10^{-7} \text{ A/cm}^2$) samples compared to the bare Ti substrate ($11.359 \times 10^{-7} \text{ A/cm}^2$). This reduction reflects the effectiveness of the coatings in preventing electrochemical reactions at the surface.

Additionally, the corrosion resistance (R_{corr}) of the CTO film was $59.062 \text{ k}\Omega\text{cm}^2$, whereas it was about $32.421 \text{ k}\Omega\text{cm}^2$ for bare the Ti substarte. This increase in R_{corr} demonstrates the enhanced ability of the coatings to resist electrochemical current. Furthermore, the corrosion rate (CR) showed the greatest reduction in the CTO film (44.36%). These findings confirm the critical role of the coatings, the advanced oxide

layers in CTO film, in reducing the corrosion rate and improving surface protection. This aligns with the protective mechanisms of oxide coatings and doped oxide layers in physiological environments.

3.2.3.1. Impedance spectroscopy analysis. The Ti substrate and CTO film exhibited significant differences in electrochemical characteristics, particularly in corrosion resistance, with notable distinctions in the compact and porous layers. The compact layer, a dense oxide layer adhering tightly to the Ti substrate metal surface, acts as a protective barrier against the penetration of corrosive solutions, as shown in Figs. 7 and 8. From the impedance spectroscopy data in Table 2, it can be seen that while the Ti substrate compact layer exhibited a very low resistance (3.59Ω) and a high capacitance ($61,400 \text{ nF}$), indicating a thin and ineffective natural oxide layer in preventing ion penetration from the solution, the CTO film compact layer demonstrated a significantly higher resistance (19Ω) and a lower capacitance (76.0 nF), reflecting a more robust and protective oxide layer.

Furthermore, the nanotubes with heterostructured structure of CTO film exhibited a resistance of 9.41Ω and a high capacitance of $21,800 \text{ nF}$, indicating the development of a heterostructured structure that increases the contact area with the environment and may influence ion absorption capacity. In contrast, Ti substrate lacked a distinct porous layer, rendering the surface susceptible to attack by corrosive solutions (Table 2). Overall, CTO film demonstrated superior corrosion resistance compared to Ti substrate due to its high-resistance compact layer and well-developed structure, effectively protecting the metal surface in harsh environments.

3.2.4. In vitro testing in SBF soaking solution

To evaluate the biocompatibility of the materials, the first method used was to examine the formation of a hydroxyapatite (HA) mineralized layer on the samples after immersion in simulated body fluid (SBF) under two different time conditions. Previous studies have demonstrated that both pure titanium surfaces are bio-inert [39,40]. Therefore, we focused solely on the properties of the CTO film after immersion in

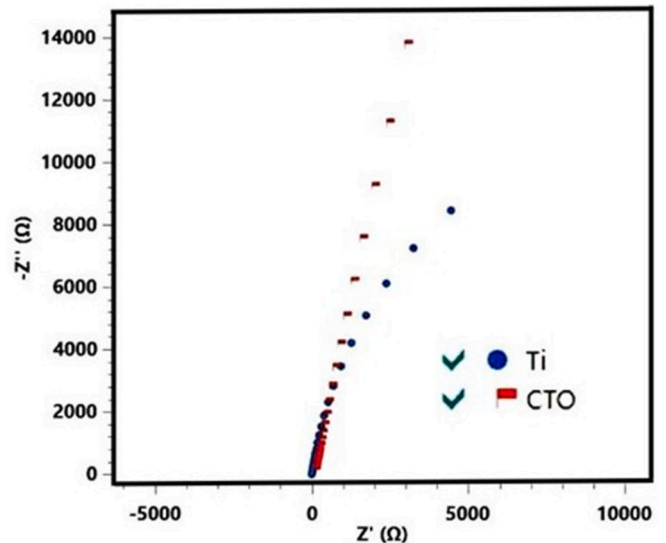


Fig. 7. Impedance spectra of the Ti substrate and the CTO film.

Table 1
Electrochemical behavior of the Ti substrate and CTO film.

Samples	E_{corr} (V)	E_{corr} (%)	i_{corr} ($\times 10^{-7} \text{ A/cm}^2$)	R_{corr} ($\text{k}\Omega\text{cm}^2$)	CR ($\times 10^{-3} \text{ mm/year}$)	CP Efficient H (%)
Ti	0.15281	0%	11.359	32.421	13.199	0%
CTO	0.2563	67.72%	6.3201	59.062	7.3439	44.36%

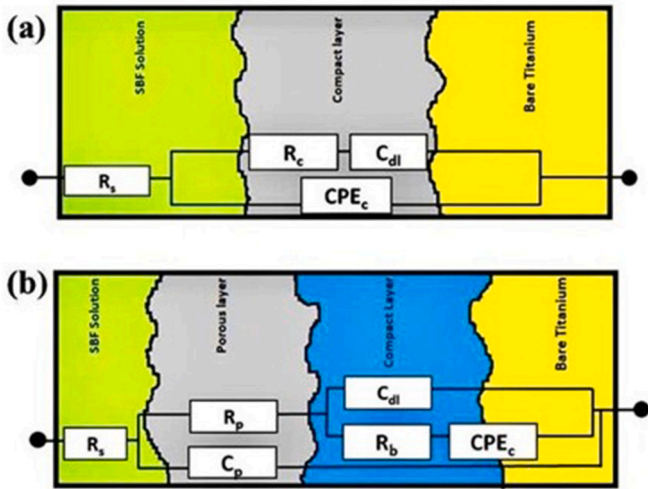


Fig. 8. Equivalent circuit modeling of (a) Ti substrate, (b) CTO film.

Table 2
Impedance spectroscopy parameters.

Sample	Layer	R (Ω)	C (nF)	Y_0 ($\mu\text{Mho}\cdot\text{s}^n$)	N
Ti	Solution	7.56			
	Compact	3.59	61,400	108	0.739
CTO	Solution	2.93			
	Porous	9.41	21,800		
	Compact	19	76.0	89.3	0.821

SBF solution. SEM was utilized to determine the formation of bone-like apatite on the CTO film soaked in SBF solution for 7 and 14 days. It can be seen that after soaking the films in the SBF solution for 7 days,

excellent HA granules emerged on the surface of the CTO film (as shown in Fig. 9a). The HA granules grew gradually with increasing soaking time in SBF. The sample soaked in SBF for 14 days, a new layer of very fine bone-like apatite was formed, covering the whole surface, the HA layer became thicker and the grain size of the HA phase increased gradually, as shown in Fig. 9b. In particular, the particles of bone-like apatite are quite porous and have a size of about $1\ \mu\text{m}$, adhering to each other and spreading across the sample surface, Fig. 9c.

To further confirm the bone-like apatite formation, EDS was employed to investigate the elemental composition of the hydroxyapatite (HA) layer, Fig. 10. It was found that a bone-like apatite layer with elemental traces of Ca, P, and O formed the surface of the CaTiO_3 film. The combination of EDS and SEM results confirms that the mineralized bone layer increases with increasing SBF immersion time. Furthermore, the Ca/P ratio increases compared to other elements. This indicates that CaTiO_3 film has high biocompatibility and meets the requirements for biomedical applications.

3.2.5. In vitro cell culture test

For materials used in implant materials and drug delivery in particular, cell growth on the material surface is a crucial and important factor. In this study, BHK cells were used to evaluate the biocompatibility of the material. This evaluation is specifically shown in Fig. 11, where the difference in cell growth on the Ti substrate and the CTO film were observed. As shown in Fig. 11, cells on both Ti substrate and CTO film exhibit good cell attachment with cell nuclei displaying uniform round morphology and being surrounded by well-defined cell boundaries. The cells show elongated and flattened morphology. This indicates that the CTO film was biocompatible surface.

Fig. 12 shows the expression of filopodia in BHK cells culturing on the Ti substrate and CTO film. On the Ti substrate, the number of filopodia is limited, mainly concentrated at both ends of the cells. The adhesion density is lower compared to the CTO film, demonstrated by the separation between cells, with limited cell-cell interactions. For the CTO film, cells exhibit a more spreading morphology with numerous

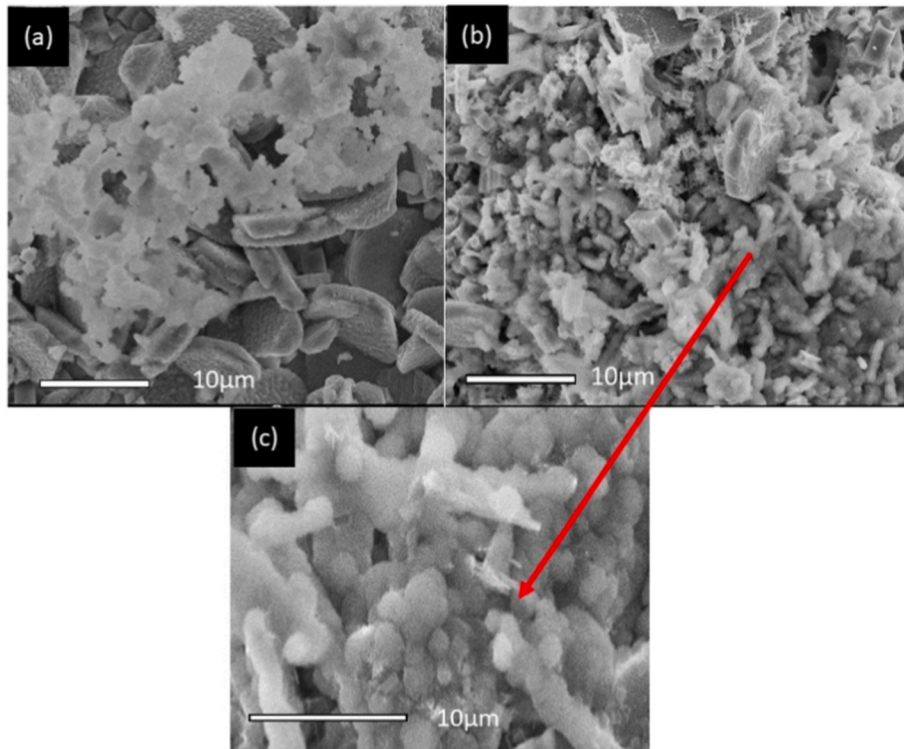


Fig. 9. SEM images of CTO films after SBF immersion. (a) 7 days, (b) 14 days, (c) High-magnification image of the bone mineral layer of CTO films after SBF immersion in 14 days.

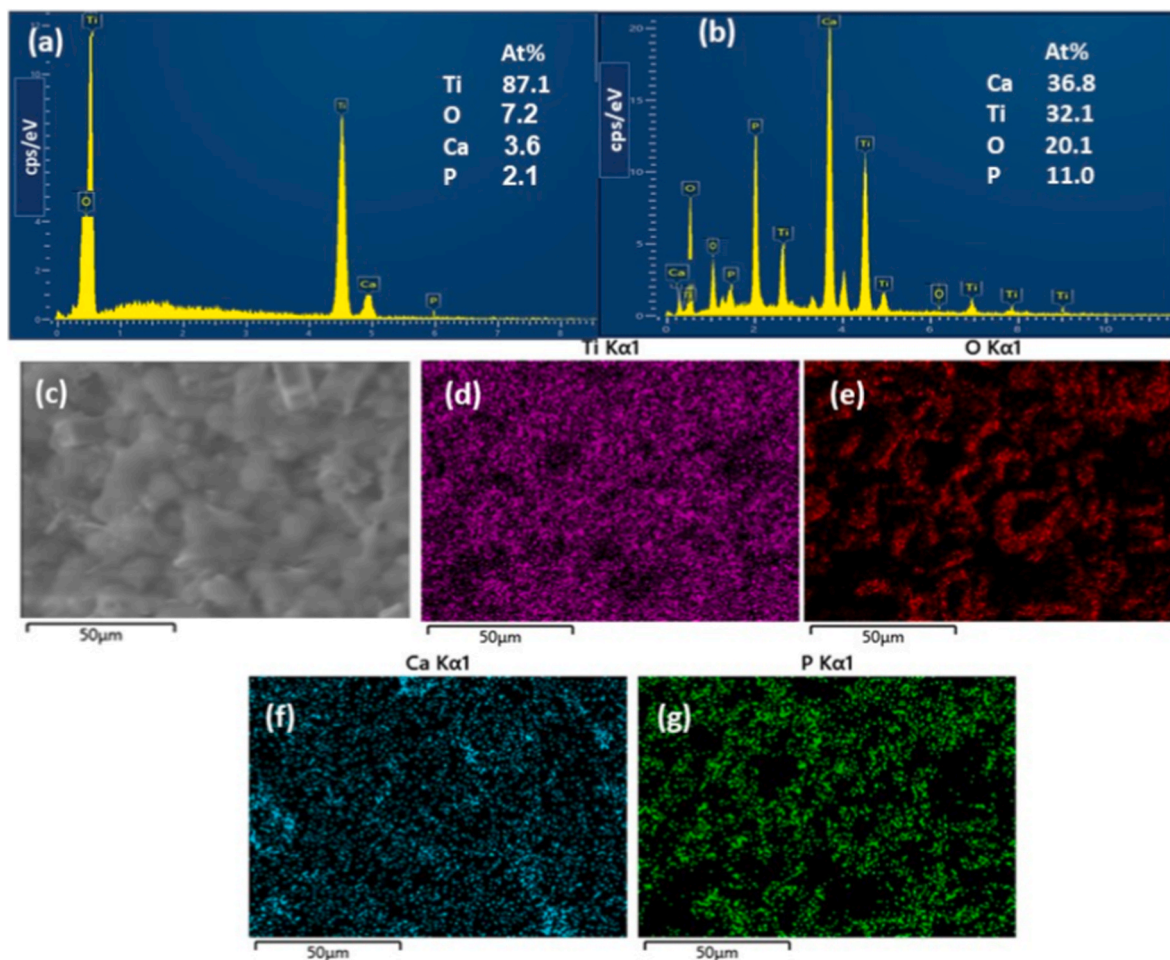


Fig. 10. EDS images of CTO films after SBF immersion in different times. (a) 7 days, (b) 14 days, (c) surface morphology, (d-g) EDS color mapping, (d) titanium, (e) oxygen, (f) calcium, and (g) phosphor. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

branches extending in multiple directions. The number of filopodia is significantly higher, appearing densely distributed around the cells. Filopodia display short-branched-multidirectional characteristics, indicating active adhesion and good interaction with the substrate. Additionally, there is evidence of intercellular connections, manifested through filopodia linking to each other, enhancing tissue formation capability. This demonstrates that the CTO film strongly stimulates filopodia development, creating more favorable conditions for cell adhesion and growth compared to the Ti substrate.

3.2.6. Drug releasing

After implantation surgery, the use of antibiotics and anti-inflammatory drugs is crucial to prevent infection, and inflammation, and to promote better integration between the bone and the implant material. Typically, these medications are administered orally or by direct injection. However, these methods often lead to drug wastage as a portion of the drug is metabolized by the liver and excreted from the body, necessitating frequent dosing. Therefore, there is a need to find a more efficient and cost-effective slow drugs releasing method. One promising approach is to use a slow drug releasing system that releases the drug directly from the implant material. This method allows for a sustained release of the drug within the implant site and prolongs the duration of drug action. In this study, we will apply a slow drugs releasing system to the CTO films. The drug loading and releasing schematic is illustrated in Fig. 13.

To confirm successful drug loading into the CTO film, confocal laser microscopy (CLMS) was employed to observe drug adsorption within the

film. Curcumin exhibits photoluminescence in the green region (550 nm) and an absorption peak at 420 nm [41]. Therefore, excitation with a 420 nm light source on the curcumin-loaded materials revealed a green signal, as observed in Fig. 14. Fig. 14a and (b) show the successful loading of curcumin into the Ti substrate and CTO film, respectively, but the CTO film exhibits a higher curcumin uptake compared to that of the Ti substrate. Following successful drug loading, curcumin releasing was conducted in simulated body fluid (SBF) as shown in Fig. 14(c and d). Comparing the samples before and after sustained release in SBF solution, a decrease in curcumin content was observed in both Ti substrate and CTO film. From the observations in Fig. 14, it is evident that both Ti substrate and CTO film are capable of curcumin uptake and releasing.

To determine whether curcumin was incorporated into the tubular structure or merely adhered to the material surface, the samples were examined using 3D CLMS, revealing the penetration of curcumin into the CTO tubular structure, as shown in Fig. 15. The 3D CLMS images were scanned from the region where curcumin fluorescence at 550 nm appeared firstly to the point where the green signal was no longer detectable on the CTO surface. The curcumin was loaded into the tubular structure to a depth of approximately 4.8 μm, confirming that the curcumin penetrated the entire length of the CTO tubes, as measured in the cross-section SEM image (Fig. 1d). Additionally, the extra amount of 0.8 μm layer could be attributed to a small amount of curcumin adhering to the surface of the CTO film during the loading process.

Comparative slow drugs releasing profiles of curcumin loaded into Ti and without CTO film are presented in Fig. 16 and releasing characteristics at various time intervals are listed in Tables 3 and 4. With the

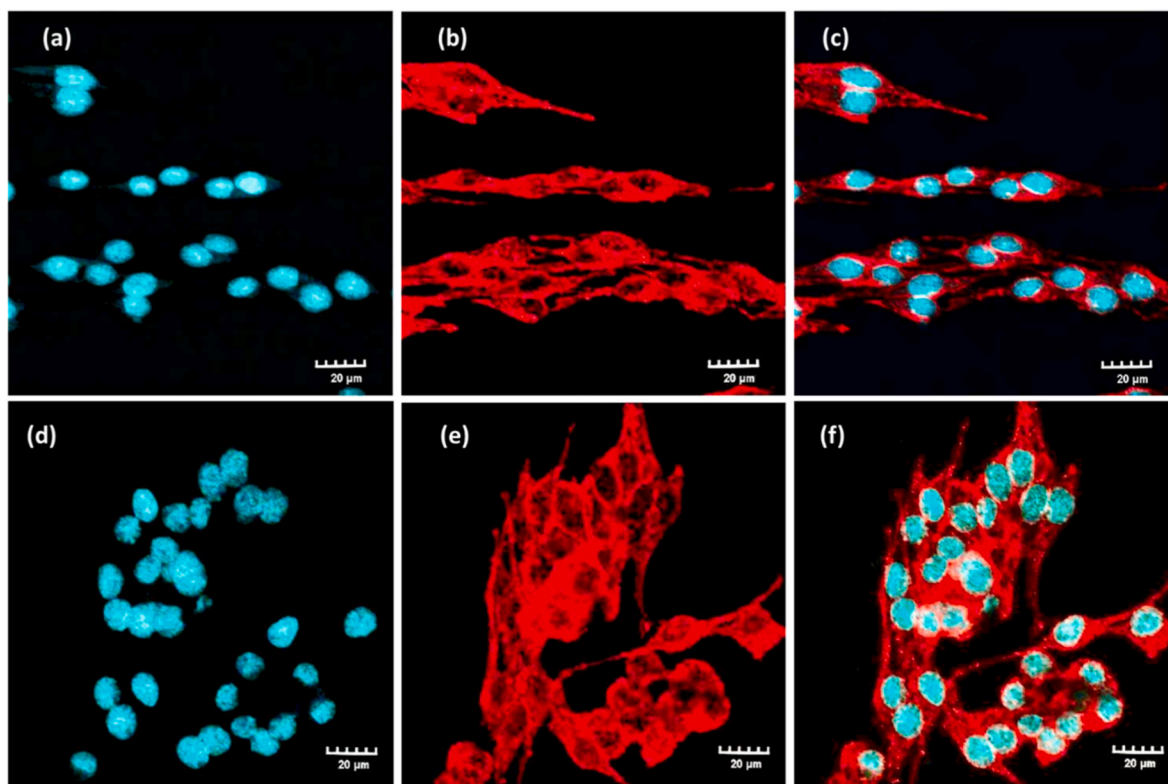


Fig. 11. CLSM images of BHK cells cultured on Ti substrate (a, b,c) and CTO film (d, e, f) after 48 h of incubation.

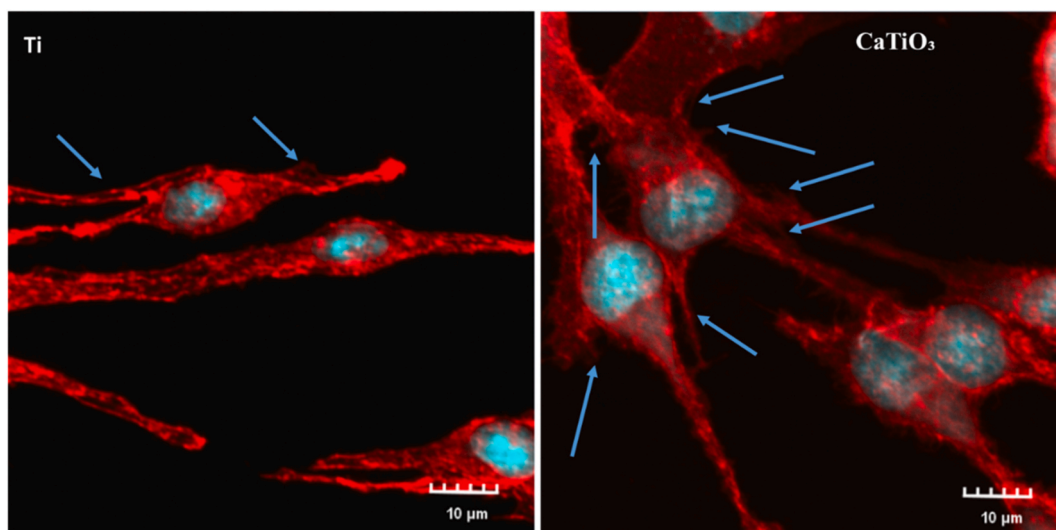


Fig. 12. CLSM images of BHK cells were captured at 40X magnification on the Ti substrate and CTO film. The arrow indicates of filopodia of the cell.

unique tubular structure of CTO film, slow drugs releasing is represented as a non-degradable slow drug releasing system. Such systems involve the transport of curcumin from regions of high concentration (CTO tubes) to regions of low concentration (surrounding PBS buffer). As a result, both samples exhibited near-complete releasing (90 -100%). However, the releasing profiles of the Ti substrate and CTO film are different. From the graphs in Fig. 16, we also observed that curcumin releasing from Ti substrate was faster compared to that of the CTO film. Specifically, the curcumin releasing rate of the Ti substrate was twice as fast as that of the CTO film, particularly within the first 6 h, where the Ti substrate and the CTO film released 48.8% and 28.54%, respectively (Fig. 16a). For slow drugs releasing systems like Ti substrate, the high

initial burst releasing means a high local drug concentration in a short period, which can cause toxicity to local tissues and also corresponds to an initial waste of the loaded drug. As shown in Fig. 16b amount of curcumin was released entirely within 6 days on the Ti substrate, whereas it was delayed until 14 days on the CTO film. The slow curcumin releasing from CTO film can be explained by its altered internal structure, which acts as restrictive barriers to interfere with the diffusion of drug molecules.

The reported values are expressions of the mean of three independent runs. The percentage of slow drugs releasing is calculated as follows:

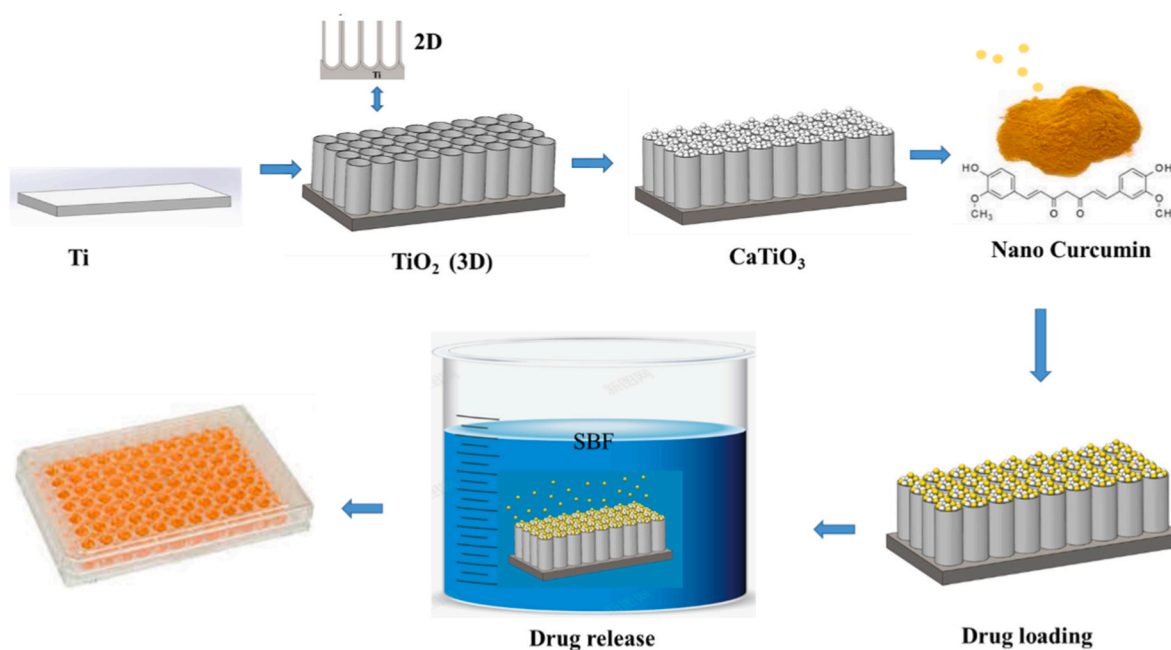


Fig. 13. Schematic representation of the in vitro curcumin release study from the CTO film.

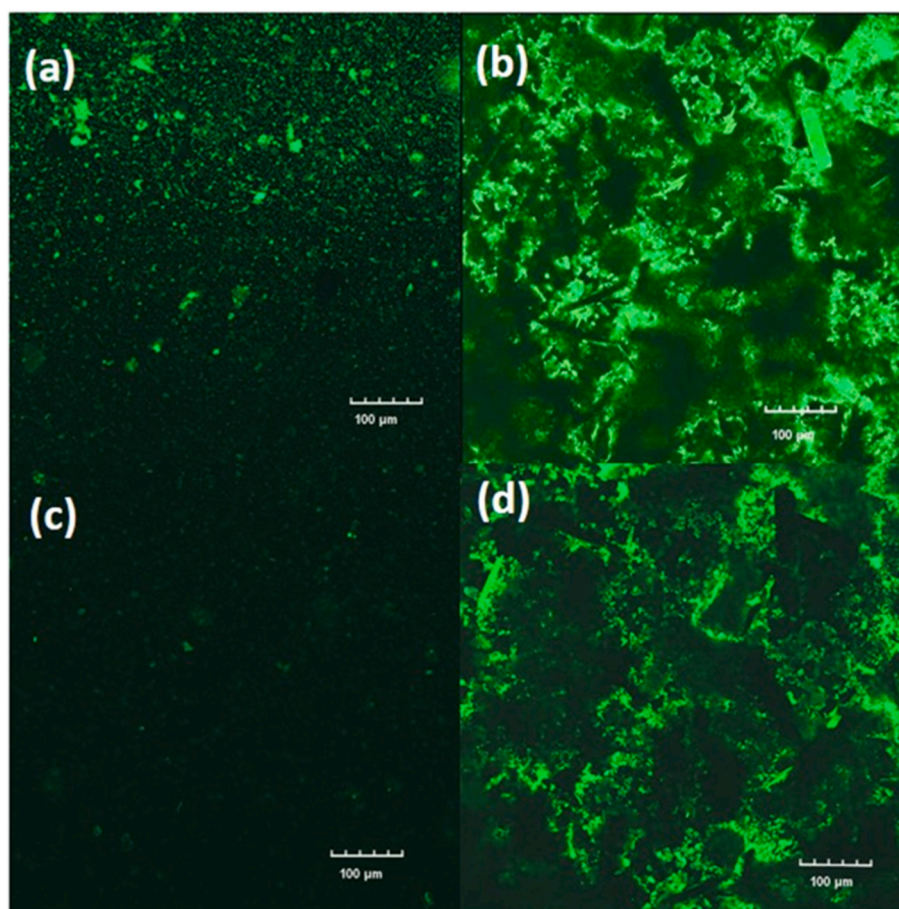


Fig. 14. CLMS images of curcumin before and after 14 days slow drug releasing on (a) Ti substrate, and (b) CTO film.

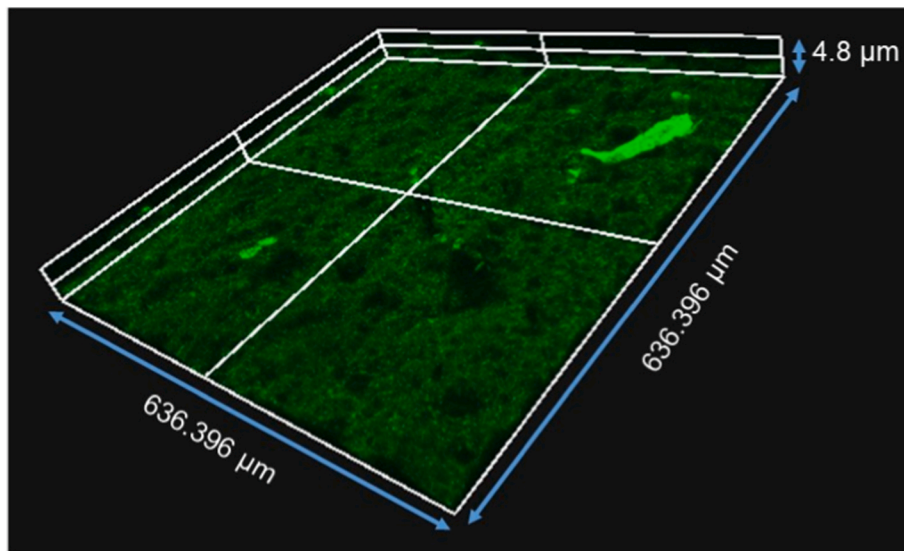


Fig. 15. 3D confocal laser microscopy (CLMS) images of curcumin distribution on the CTO film.

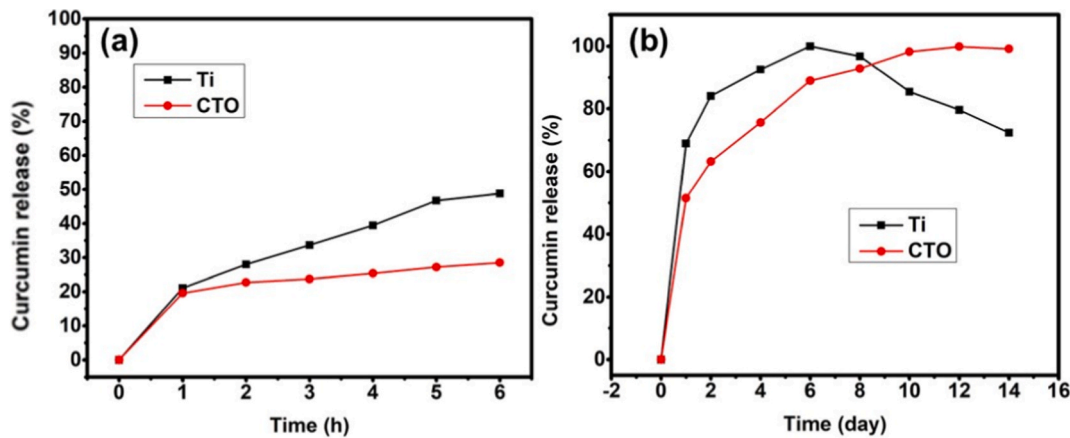


Fig. 16. Slow curcumin releasing graph of Ti substrate and CTO film.

Table 3
Hourly-based slow curcumin releasing of the Ti substrate and CTO film.

Samples	Amount of curcumin releasing		Curcumin releasing (%)	
	Ti	CaTiO ₃	Ti	CaTiO ₃
1 h	0.064	0.060	21.12	19.63
2 h	0.085	0.069	28.03	22.76
3 h	0.102	0.072	33.69	23.75
4 h	0.119	0.077	39.49	25.40
5 h	0.142	0.083	46.72	27.22
6 h	0.148	0.087	48.8	28.54

$$\text{Percentage released (\%)} = \frac{\text{Amount of curcumin released}}{\text{Total curcumin in CTO}} \times 100\% \quad (1)$$

These results clearly demonstrate that the CTO structure can enhance both its curcumin loading and release characteristics, making it more suitable for bone implant applications. Previous studies using structural modifications of Ti substrate and TiO₂ nanotube, by controlling the diameter and length of nanotubes. This motivated our group to explore other concepts to reduce the initial high burst releasing, by improving the TiO₂ substrate, a new film with a compatible Ca content is created, as

Table 4
Day-based slow curcumin releasing of the Ti substrate and CTO film.

Samples	Amount of curcumin releasing		Curcumin releasing (%)	
	Ti	CaTiO ₃	Ti	CaTiO ₃
1 day	0.209	0.156	68.92	51.50
2 days	0.255	0.191	84.06	63.15
4 days	0.281	0.229	92.53	75.65
6 days	0.303	0.270	100	88.95
8 days	0.293	0.282	96.74	92.87
10 days	0.219	0.298	72.39	98.22
12 days	0.168	0.303	55.39	99.87
14 days	0.111	0.301	36.48	99.17

well as forming a heterostructure inside the nanotube and packaging the drug inside these unique structure. The heterostructure of CTO film can provide advanced performances, including further reduced initial burst releasing, and extended slow drugs releasing to several months. In this model, drug curcumin is used but CTO film can be loaded with a variety of therapeutics like proteins, antibiotics, anti-cancer drugs, and growth factors for specific bone therapies including treatment for inflammation, infection, poor bonding and primary or secondary bone cancers.

There are various models for describing drug release kinetics. Among

Table 5

Initial drug release phase.

Samples	n	k	R ²	Transport mechanism
Ti	0.482	0.206	0.991	Anomalous (non-Fickian)
CaTiO ₃	0.202	0.195	0.983	Fickian diffusion

Table 6

Summarized cucumin release stage.

Phase	Model	Key parameter
Initial release (≤6 h)	Korsmeyer-Peppas	n ≈ 0.2 (Fickian diffusion)
Sustained release (14 day)	Weibull	β (Combined mechanism)

them the Ritger-Peppas and Korsmeyer-Peppas models indicated the drug release from materials systems and established an exponential relationship between drug release and time as describing in equation (2) [42].

$$\frac{M_t}{M_\infty} = Kt^n \quad (2)$$

Overall, the equation Eq. (2) contribute to distinguishing the release profiles of drug by first-order or zero-order. For a film, the exponent of release $n = 0.5$, the system is followed by Fickian with diffusion driving first-order release. In the case $n = 1$, the model is followed by non-Fickian and match up with zero-order drug delivery, which is controlled by forces like swelling or polymer chain relaxation. If $0.5 < n < 1$, drug release is characterized by a both diffusion and swelling. M_∞ is the amount of drug at equilibrium, M_t is the amount of drug released over time, K is the release velocity constant, and n is the exponent of release.

The kinetic cucumin release characteristic at different stage was showed in Table 5.

Initial cucumin release phase (0–6 h): Both Ti and CaTiO₃ film fitted well with the Korsmeyer-Peppas model. The bare Ti substrate showed a high release rate (K), likely governed by rapid desorption of weakly bound cucumin on the flat Ti surface. Conversely, the CTO film $n \approx 0.2$ indicates Fickian diffusion [43]. This confirms that the initial release is governed by passive diffusion driven by the concentration gradient through the heterostructured CaTiO₃ matrix without significant matrix swelling or erosion.

Sustained cucumin release phase (1–14 days): the Korsmeyer-Peppas model has inherent limitations. The previous publications confirms that this model is strictly valid only for the first 60% of drug release ($M_t/M_\infty \leq 0.6$) [43,44]. For complete release profiles extending to 14 days, the Weibull model was used as follows [45,46]:

$$F = 100 \times \left(1 - e^{-\left(\frac{t}{\tau}\right)^\beta} \right) \quad (3)$$

where F is the fraction of drug released at time t , τ is the time for 63.2% release, and β is the shape parameter [44].

In this work, the Weibull model is particularly appropriate for the followed reasons: firstly, it has no time-limit restrictions and fits complete release curves including the plateau phase [45]. Secondly, it has been successfully used to describe sustained release over multi-week periods [46]. Finally, the shape parameter β provides mechanistic insight: $0.75 < \beta < 1$ indicates a combined diffusion-relaxation mechanism, while $\beta < 0.75$ indicates Fickian diffusion [47]. Overall the cucumin release stage was summarized in Table 6.

Interestingly, the curcumin-loaded CTO film exhibited a highly sustained release profile extending up to 14 days. Given the open-ended morphology of the synthesized heterostructure, this prolonged retention cannot be described solely by physical entrapment or Fickian

diffusion. Instead, it is predominantly governed by robust interfacial chemical interactions between the curcumin molecules and the CTO matrix. Firstly, the surface of hydrothermally synthesized CTO is inherently terminated with abundant hydroxyl groups ($\equiv \text{Ti}-\text{OH}$ and $\equiv \text{Ca}-\text{OH}$). These sites form extensive hydrogen-bonding networks with the phenolic hydroxyl and carbonyl functional groups of curcumin. Secondly, curcumin is well-known for its prominent keto-enol tautomerism, which readily transitions into an enolate form capable of acting as a strong chelating agent. These enolate groups undergo surface complexation via coordination bonds with the transition metal Ti^{4+} ions and alkaline earth Ca^{2+} ions exposed on the heterostructure walls. The formation of these stable surface complexes acts as an energetic barrier, significantly anchoring the curcumin molecules and preventing an immediate burst release. Consequently, the desorption of chemically bound curcumin from the internal surfaces of the heterostructure serves as the rate-limiting step, resulting in a well controlled, extended release profile which is suitable for biomedical applications.

4. Conclusion

In summary, we report the hydrothermal preparation of CTO film on the TiO₂ nanotube template and investigating the characteristics of the CaTiO₃ film for potential application in biomedical implants and slow drugs releasing. The CTO film exhibits superior properties, including an excellent tubular structure, wettability, corrosion resistance, and biocompatibility, as demonstrated by tests in SBF solution and BHK cells. The beneficial of the CTO film is its good biocompatibility and slow drugs releasing capability with a prolonged releasing time up to 14 days which it can be applied to biomedical implants with controlled drugs releasing.

CRedit authorship contribution statement

Nguyen Thi Thanh Tuyen: Data curation, Methodology, Writing – original draft. **Le Van Toan:** Investigation, Methodology, Visualization. **Pham Van Huan:** Data curation, Formal analysis, Software. **Pham Van Hao:** Formal analysis, Methodology, Visualization. **Tran Thi Trang:** Conceptualization, Methodology, Validation. **Le Thi Bang:** Investigation, Methodology, Resources. **Nguyen Van Toan:** Methodology, Validation, Visualization. **Nguyen Ngoc Thang:** Data curation, Formal analysis, Methodology. **Hoang Van Vuong:** Formal analysis, Methodology, Software. **Ta Quoc Tuan:** Investigation, Resources, Software. **Le Thi Tam:** Conceptualization, Methodology, Resources. **Cao Xuan Thang:** Data curation, Formal analysis, Investigation. **Vuong-Hung Pham:** Project administration, Resources, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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