Studies of magnesium – hydroxyapatite micro/nano film for drug sustained release

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Abstract
It is challenging to fabricate the bioactive films containing magnesium (Mg) particles to obtain a film with a porous structure. These microporous structures facilitate the diffusion of the drug covered by the Mg-HA film to achieve sustainable drug release. Herein, ciprofloxacin hydrochloride (CIP) film as the drug representative is obtained by low energy electron beam deposition (LEBD) to verify the sustained release effect of Mg-HA film. Therefore, the four-layer composite films with a distribution of the CIP are obtained using the layered growth of CIP film and Mg-HA film by the PLD-LEBD coupling technology. The results showed that Mg-HA film not only prolonged the CIP release period, but also enhanced the drug release in the middle and late stages.

Introduction
In the previous works [1], it was found that porous structure appeared on the surface of Mg-HA film after soaking in simulated body fluid (SBF) for seven days. This is due to the precipitation of Mg in Mg-HA film and the formation of interconnected pores similar to the network structure. Besides, it has been proved in previous studies that low-energy electron beam deposition technology (LEBD) can effectively protect the original structure of materials from destruction, such as the deposition of polymer materials (polylactic acid, polycaprolactone, polyvinyl chloride, etc.) and some drugs (ciprofloxacin hydrochloride, norfloxacin, etc.) [2 – 5]. Therefore, ciprofloxacin hydrochloride (CIP) was used as the target drug to construct multilayer drug-loaded composite film by PLD-LEBD coupling technology, and the sustained release behavior of CIP in the composite films in phosphate buffer saline (PBS) was evaluated. The sustained release of drug therapeutics for bone defect restoration has become an attractive design strategy for accelerating the rate of bone healing and for reducing the risk of a chronic wound.

Materials and methods
Mg-HA film was prepared by PLD (λ = 1024 nm) with a mixture of magnesium and hydroxyapatite (mass ratio = 2:1) as the target material. The thickness of Mg-HA film could be controlled by adjusting the deposition time. CIP film was formed by continuous irradiation of LEBD on the target. The target material was composed of CIP powder (5 mg), and the target area was in the irradiation range of the electron beam. Detailed deposition parameters and procedures are presented in paper [5]. Multilayer composite films were prepared layer by layer by PLD-LEBD coupling technique.

Results and discussions
The four-layer composite film was immersed in PBS for different times. Then the antibacterial performance was tested with Staphylococcus aureus as strains, and CIP film as a control

group. As can be seen from the diameter of the bacteriostatic zone in Fig. 1a, the diameter of the inhibition ring of CIP film reached 29.45 ± 0.74 mm before soaking. However, there was no obvious bacteriostatic ring after soaking for 3 days, indicating that the CIP film showed a burst release at the initial stage of soaking. The surface of CIP film became smooth after soaking (Rq value drops from 54.6 ± 0.3 nm to 30.1 ± 0.5 nm), which can be obtained by SEM and AFM images. In contrast, the four-layer composite film showed a sustained drugs release pattern. These pores played a vital role in the release of the third layer (CIP film).

The kinetic release behavior of CIP in the four-layer composite film is investigated in PBS. Fig. 1b shows the kinetic release curve of CIP during the four-layer composite film soaked in PBS for 14 days and the concentration-absorbance standard curve of CIP in PBS. According to the CIP kinetic release curve in Fig. 1b, the CIP release can be divided into two stages: the first stage is soaking for 0 ~3 days, and the first layer (CIP film) is mainly released; The second stage is soaked for 3 ~ 14 days. With the gradual degradation of the second layer (Mg-HA film), the third layer (CIP film) enters the release stage and the release rate is significantly lower than that of the first layer (CIP film). Therefore, it can be inferred that the degradation process of Mg in Mg-HA film plays a decisive role in the kinetic release of CIP.

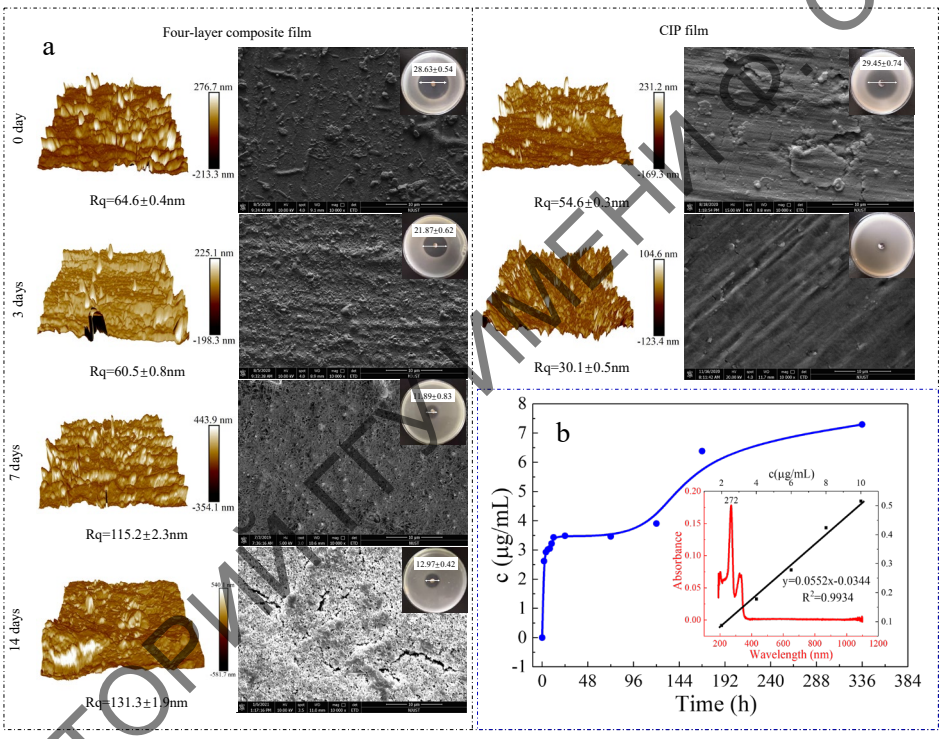

Fig. 1. (a) AFM and SEM morphology and antibacterial properties of the four layers of composite film soaked for different times with CIP film as the control group; (b) The kinetic release curve of CIP in the four layers of composite film and concentration-absorbance standard curve of CIP in PBS

Conclusion

In this study, Mg-doped hydroxyapatite (Mg-HA) films with uniform distribution of Mg particles were obtained by pulsed laser deposition (PLD). Mg in Mg-HA membrane was preferentially degraded in simulated body fluids for ion exchange, thus forming microporous structures on the surface of Mg-HA film. Thus, as the drug representative, ciprofloxacin hydrochloride (CIP) film was obtained by low energy electron beam deposition (LEBD) to verify the sustained release effect of Mg-HA film. Herein, four-layer composite films with a distribution of the CIP were obtained using the layered growth of CIP film and Mg-HA film by the PLD-LEBD coupling technology. The results showed that Mg-HA film not only prolonged the CIP release period, but also enhanced the drug release in the middle and late stage.

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