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A Novel Hollow Hydroxyapatite Microspheres/Chitosan Composite Drug Carrier for Controlled Release

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Abstract: A novel composite drug carrier with excellent sustained and pH-sensitive release performance was prepared by mixing hollow hydroxyapatite (HA) microspheres and chitosan solution with pH-sensitive characteristics. The hollow HA microspheres with mesopores filled on their multilayered spherical shell were obtained by converting borate glass with a novel composition of $19Na_2O$-17CaO-$64B_2O_3$ (wt%). The structure, phase composition and morphology of HA microspheres were characterized by SEM, SEM-EDS, XRD, FTIR and N_2 adsorption-desorption measurements. The results indicated that the HA microspheres were B-type carbonated HA with hollow structure, in which the carbonate ions occupied the phosphate sites. The drug release results indicated that the HA microspheres generated burst release at initial stage. Coating the hollow HA microspheres with chitosan (CS) reduced the vancomycin release amount and release rate significantly. Meanwhile, the release profile of vancomycin into PBS with different pH value indicated that the CS-coated composite drug carrier shows pH-sensitive release property. The cumulative percentage of vancomycin released into PBS from the CS (20 g/L)-coated composite drug carrier was 85.63%, 65.85% and 71.85% for pH 6.0, 7.4, 8.5, respectively.

Key words: hollow hydroxyapatite (HA) microspheres; composite drug carrier; pH-sensitive; chitosan

The regeneration of large bone defects resulting from trauma, malignancy or congenital diseases represents a common and significant clinical problem[1-2]. Autografts are the gold standard for treatment but they suffer from many problems such as limited availability, donor site morbidity and increased surgery time. Allografts are alternatives, but they are expensive and carry the risk of disease transmission and adverse host immune reaction. These problems associated with autografts and allografts have increased the need for synthetic bone graft substitutes[3]. At the same time, researchers are striving to develop new drug delivery system, which need possess many properties, such as the biocompatibility, bioactivity, targeted and controlled drug delivery[4].

As the main inorganic component of bone and teeth, hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$, HA] has favorable bioactivity and biocompatibility as well as the ability to have chemical bond with natural bone and has been widely applied in defect replacement and repairing process of bone tissues in the clinical[5]. Among the different HA forms, the hollow microspheres have proven to be ideal vehicles for many delivery applications due to their good ability to encapsulate more drugs and sustained drug release characteristics[6]. Recently, we developed a convenient method to prepare hollow HA microspheres at room temperature by converting borate glass[7]. The method has several distinct advantages. Firstly, the HA products prepared by the glass conversion technique have biomineralization effect with a higher bioactivity than the HA products synthesized by other methods, which will benefit the growth of biological cells. Then, the HA products retain the same external shape and dimensions as the starting glass microspheres, which is beneficial to certain applications when precontrolled size and shape are desirable[7]. The hollow HA microspheres prepared by the glass conversion technique have a high specific surface area and a porous shell wall that can provide reservoirs for loading drugs[8]. Moreover, the preparation process is simple and low cost, and hence can be easily scaled up to meet industrial needs.

It is well known that the pH in tumors and inflammatory tissues is lower than those in blood or normal tissues, which also shows variation at osseous pathological site and

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various periods[9]. It was reported that the pH around the ruffled border of osteoclasts is about 4.0 during bone remodeling and the local environment of fracture hematoma changes from acidic initially to alkaline ultimately as the healing progresses[10]. As a result, it is important to prepare a pH-sensitive drug carrier for bone-repairing to control the drug release process. Chitosan (CS), a natural-based polymer obtained by alkaline deacetylation of chitin, has attracted more attention recently owing to its biodegradable, biocompatible, nonantigenic, and nontoxic properties[11]. Many pharmaceutical studies indicated the chitosan is a useful vehicle for controlled release of drugs. It can also be used as a binder for drug carrier materials to improve their properties[12]. Besides, chitosan hydrogels also show temperature and pH sensitivity. At 37℃, chitosan solutions can change into gelation as the pH increases to 6.5 or higher, and hence can be properly used as pH-controlled release drug carrier[13].

This study is aimed to prepare a novel hollow HA microspheres/chitosan composite drug carrier and investigate its drug release behavior. Herein, we prepared a new hollow HA microsphere with mesopores filled on their multilayered spherical shell by converting borate glass microspheres in phosphate solution. The novel borate glass composition of $19Na_2O$-17CaO-$64B_2O_3$ (wt%) was based on a number of glass composition experiments and, then further synthesized a novel hollow HA microsphere/chitosan composite drug carrier. The chitosan solution with pH-sensitive characteristics was used to coat the hollow HA microspheres to modify its drug-release performance and obtain the pH-controlled release performance at the same time. Furthermore, we made definite analysis of the principle and mechanism for the release behavior of vancomycin from the drug carrier. Vancomycin was used in this study because of its good function on the treatment of bone disease and excellent bonding properties with HA.

1 Materials and methods

1.1 Preparation and characterization of hollow HA microspheres

Hollow HA microspheres were prepared by reacting borate glass microspheres in an aqueous phosphate solution as described in our previous study[8]. Briefly, borate glass with a novel composition $19Na_2O$-17CaO-$64B_2O_3$ (wt%) was prepared by melting reagent grade Na_2CO_3, $CaCO_3$ and H_3BO_3 (AR, Shanghai, China) in a Pt crucible at 1150℃ for 30 min, and quenching the melt between cold stainless steel plates. Particles with single distribution of 100–150 μm were obtained by grinding the glass in a hardened steel mortar and pestle, and sieving through 100 and 150 mesh sieves. Glass microspheres were obtained by the method of spray ball in flame. Hollow HA microspheres were obtained by reacting the borate glass microspheres for 2 d in 0.2 mol/L K_2HPO_4 solution at 37℃ with a pH 9.0. In converting process, 1 g glass microspheres were placed in 100 mL solution. The converted microspheres were washed three times with distilled water, soaked in anhydrous ethanol to displace residual water and dried at least 12 h at 60℃, then heated 2 h at 600℃.

Characterization of the converted microspheres was performed using the methods described in our previous studies[14]. Briefly, the microstructure of the surface and cross-section of the microspheres were examined using scanning electron microscope (SEM, S4700, Japan). Both of the dried and heat-treated microspheres were examined by X-ray diffraction (XRD, D/max 2550V, Japan) to identify the phase composition. FTIR spectra (EQUINOXSS/ HYPERION2000, German) were used to evaluate the functional groups of samples in the wavenumber range of 400–4000 cm^{-1}. N_2 adsorption-desorption isotherms were obtained on a SA3100 automatic surface area and porosity analyzer (Beckman Coulter, SA3100, USA). Brunauer, Emmett, and Teller (BET) and Barrett, Joyner, and Halenda (BJH) analyses were used to determine the parameters of pore structure.

1.2 Loading the microspheres with vancomycin

After sterilization by soaking in anhydrous ethanol and drying in an incubator at 120℃, the hollow HA microspheres were loaded with vancomycin (USP, Shanghai, China) using vacuum-assisted method[8]. In loading process, 100 mg of hollow HA microspheres were placed in a 1 mL centrifuge tube, and 500 μL of vancomycin solution, formed by dissolving 10 mg vancomycin in 5 mL deionized water, was pipetted onto the microspheres. The system was placed into a vacuum drying oven for 6 h at 30℃ to replace the air with the vancomycin solution in the hollow HA microspheres and dried. The vancomycin solution diffused into the inner cavity of the hollow HA microspheres under the pressure. Vancomycin can be combined with the HA crystals by the hydrogen bond, which is formed by the carboxyl groups on the surface of the vancomycin and the active hydroxyl groups on the surface of the hydroxyapatite crystals. In addition, the solution was dried to ensure that the vancomycin loaded on the microspheres completely. The vancomycin-loaded microspheres were used immediately.

1.3 Preparation and characterization of the composite drug carrier

The release behavior of vancomycin from the as-prepared microspheres was modified by coating the vancomycin-loaded microspheres with chitosan. In coating process, 500 μL chitosan solution was added to 100 mg microspheres in a flat-bottom beaker (2.5 cm in diameter).

The system was dried at 40℃ for 6h in a vacuum drying chamber after the microspheres distributed in chitosan solution uniformly. Two different concentrations of the chitosan solution were used to form coatings with different thicknesses. Both of the composite drug carriers were examined by X-ray diffraction (XRD, D/max 2550 V, Japan) to identify the phase composition. FTIR spectra (EQUINOXSS/ HYPERION2000, German) were used to evaluate the functional groups of samples. The microstructure of the surface and cross-section of the composite drug carrier were examined using scanning electron microscopy (SEM, S2360, Japan).

The chitosan solution was prepared using the method described in our previous studies[15]. Briefly, chitosan (95% deacetylated, Shanghai, China) powder was dissolved in 1.0 mol/L acetic acid (20 g/L、30 g/L) and the mixture was stirred for 1 h, after which it was stored at 4℃. Then a solution composed by β-glycerophosphate (AR, Shanghai, China) in deionized water (560 g/L) was prepared. Finally, the chitosan solution was mixed with the β-glycerophosphate solution (ratio=9:1 by volume) and the final solution was stored at 4℃.

1.4 Measurement of drug release behavior *in vitro*

In measuring the release behavior of vancomycin from the microspheres, 10 mL of PBS was added to 100 mg microspheres (coated with chitosan or uncoated) in a centrifuge tube, and then incubated at 37℃. At selected times, then 3 mL PBS solution was taken-off and replaced by 3 mL fresh PBS respectively. The amount of vancomycin released into PBS was assayed by UV/Vis spectroscopy at the wavelength of 280 nm[16].

To investigate the pH-sensitive drug release behavior of the CS-coated composite drug carrier, 100 mg hollow HA microspheres (coated with chitosan) were firstly soaked into 10 mL PBS (pH=6.0, 7.4 and 8.5) at 37℃. At different interval, then 3 mL PBS solution was taken-off and replaced by 3 mL fresh PBS respectively. The amount of vancomycin released into PBS was assayed by UV/Vis spectroscopy at the wavelength of 280 nm.

The data was expressed as mean ± standard deviation (SD) for all experiments and was analyzed using one-way ANOVA with a post hoc test, where $P<0.05$ was considered statistically significant.

2 Results and discussion

2.1 Characteristics of the hollow HA microspheres

SEM images of the as-prepared microspheres are shown in Fig. 1. The cross-section of the microspheres in the inset of Fig. 1 confirmed the hollow structure. Fig. 2 shows the surface morphology of the as-prepared microspheress-intered at different temperatures. It can be clearly observed that the surface of the microspheres treated at 60℃ is composed by the HA sheets as indicated in the high magnification SEM image (Fig. 2(a), inset), while the surface of the microspheres treated at 600℃ is composed by the globular HA particles as shown in the high magnification SEM image (Fig. 2(b), inset).

According to the International Union of Pure and Applied Chemistry, the data shown in Fig. 3(a) suggested that the fabricated hollow HA microspheres exhibit the similar isotherms of type IV with type H1 hysteresis loop deriving from particle aggregates with slit-shaped pores in the range of (0.75–1.0)P/P_0, indicating an typical mesoporous structure with good pore accessibility[17-18]. Calculated from the adsorption-desorption branches of the isotherms using the BJH method, the pore size distribution ranges from meso-scale to macro-scale in a range of about 2–75 nm (Fig. 3(b)). The specific surface area and pore structure parameters of the microspheres were listed in Table 1. The specific surface area (SA) and the pore volume (PV) of the microspheres treated at 60℃ are 55.32 m^2/g and 0.21 cm^3/g, respectively, which is higher than that of the microspheres treated at 600℃ (31.17 m^2/g, and 0.17 cm^3/g respectively) However, The mean pore size (PS) of the microspheres treated at 60℃ was 15.38 nm compared to that treated at 600℃ (28.29 nm). It is because that the HA sheets shrink into together under 600℃, which lead to the higher mean pore size of the microspheres.

XRD patterns of the microspheres sintered at different temperatures are shown in Fig. 4(a), which show

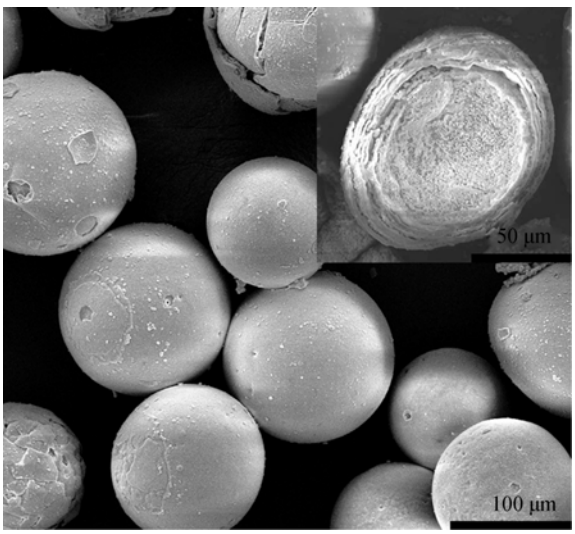

Fig. 1 SEM image of the as-prepared microspheres with a cross-section in the inset

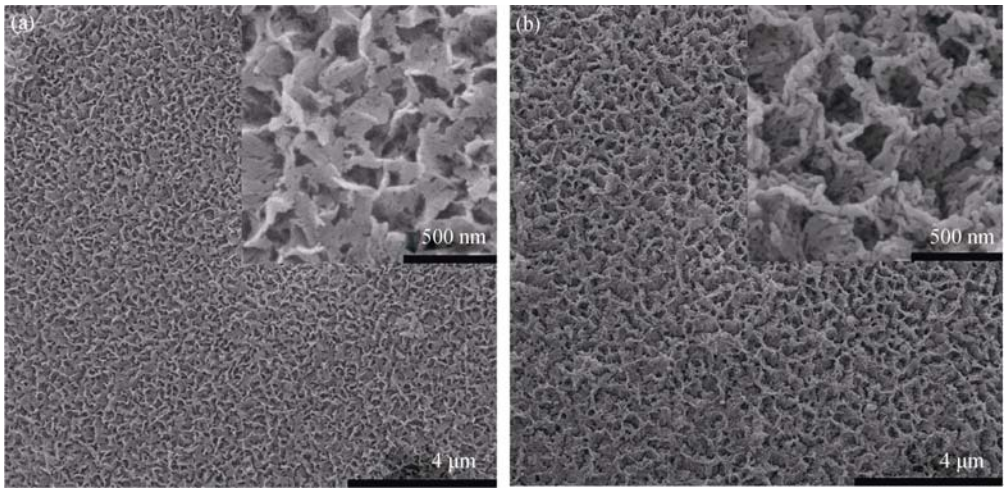

Fig. 2　Surface SEM images of the hollow HA microspheres
(a) Dried at 60℃; (b) Sintered at 600℃
The inset in (a) and (b) show the high magnification image of the surface

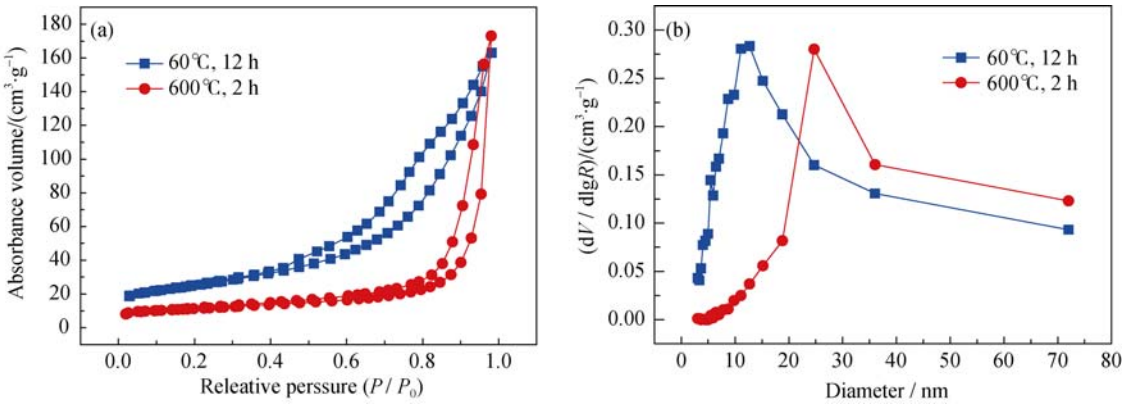

Fig. 3　The N_2 adsorption–desorption isotherm (a) and the pore size distribution (b) of the microspheres treated at different temperatures

Table 1　The surface characteristics and pore structure parameters of the microspheres

Sample	SA/($m^2 \cdot g^{-1}$)	PV/($cm^3 \cdot g^{-1}$)	PS/nm
60℃	55.32	0.21	15.38
600℃	31.17	0.17	28.29

characteristic peaks assigned to HA. Briefly, the XRD patterns of the dried (60℃, 12 h) microspheres showed no obvious peaks, indicating that the microspheres were poorly crystallized or the crystallite size of the HA particles was on a nanometer scale, or a combination of both, which was corresponding to the sheet particles seen in the SEM image (Fig. 2(a)). After heat treatment (600℃, 2 h), the sharp diffraction peaks corresponding to HA (JCPDS72-1243) can be clearly observed, indicating that the crystallinity was indeed enhanced greatly. The broaden diffraction peaks indicated that the HA was composed of crystals in nanometer-size, which was corresponding to the globular HA particles seen in the SEM image (Fig. 2(b)). Our previous study showed that the crystallinity of microspheres is low under the heat-treatment temperature below 60℃ and the HA products will be decomposed to tricalcium phosphate (TCP) under the heat-treatment temperature higher than 600℃[19]. FTIR spectra of the microspheres sintered at different temperatures are shown in Fig. 4(b), from which the peaks originated from PO_4^{3-} and OH^- groups can be observed. Specifically, the band at 3572 cm^{-1} in the spectrum was assigned to the OH–group in hydroxyapatite (600℃, 2 h). The PO_4^{3-} bands at 1039, 607, 572, and 472 cm^{-1} were also present in the spectrum (600℃, 2 h). These OH^- apatite bands and PO_4^{3-} bands can be assigned to crystalline calcium hydroxyapatite. There is no obviously peak at 3572 cm^{-1} in the spectrum when heated at 60℃.The bands at 3440 and 1639 cm^{-1} were assigned to water absorption. The bands at 1459, 1407 in the sintered (600℃, 2 h) spectrum were assigned to the CO_3^{2-} group of B-type carbonated HA[20]. These ions should be present in HA as lattice substitutions because the XRD results did not show any crystalline carbonate salts. The presence of CO_3^{2-} group in HA lattice may be

due to the presence of dissolved CO_2 from atmosphere.

The EDS measurement was carried out to investigate the composition of the as-prepared microspheres. The results indicate that the ratio of Ca/P was about 1.93, which was higher than 1.67 -the Ca/P ratio of the stoichiometric HA, as shown in Fig. 5, The higher calcium content may contribute to the degradation of the hollow HA microspheres after it was implanted, which can benefit the bioactivity of the carrier. Our previous work showed that the ratio of Ca/P of the hollow HA microspheres prepared by a lithium-calcium-boron glass with a composition of $10Li_2O$-$15CaO$-$75B_2O_3$ (wt%) was about 1.47, which was lower than that of the stoichiometric HA[14]. The higher ratio of Ca/P in this study may be attributed to the higher calcium component content (17%) in borate glass. However, there is no obviously distinction about the calcium component content between them. Therefore, the higher calcium content may mainly because the network structure of the borate glass which was adjusted due to the higher sodium component and need further study.

2.2 Characteristics of the hollow HA microspheres/ chitosan composite drug carrier

XRD patterns of the hollow HA microspheres/chitosan composite drug carrier are shown in Fig. 6(a), which are similar to the pure hollow HA microspheres. Diffraction peaks of the main crystal planes, taking (002), (211), (130), (222) and (213) for instance, were all detected. The FTIR spectrum of the hollow HA microspheres/ chitosan composite drug carriers are shown in Fig. 6(b), from which the peaks originated from PO_4^{3-} and OH^- groups can also be observed. Specifically, The absorption peaks of OH^- bands at 3572 cm^{-1} and PO_4^{3-} bands at 1039, 607 and 572 cm^{-1} in the spectrum were weakened with increasing the concentration of the CS coating solution. The absorption peak of absorbed water at 3440 cm^{-1} of the composite drug carrier were enhanced compared to that of the hollow HA microspheres.

SEM images of the surface and the cross-section of the composite drug carrier are shown in Fig. 7(a)-(d). It can be observed that both of the CS (20 g/L)-coated and the CS (30 g/L)-coated composite drug carrier show the composite aggregates. In addition, owing to the strong stickiness caused by chitosan during the drying process, both the surface and the cross-section show only slightly difference between the CS (20 g/L)-coated and the CS (30 g/L)- coated composite drug carrier. Theoretically, the different

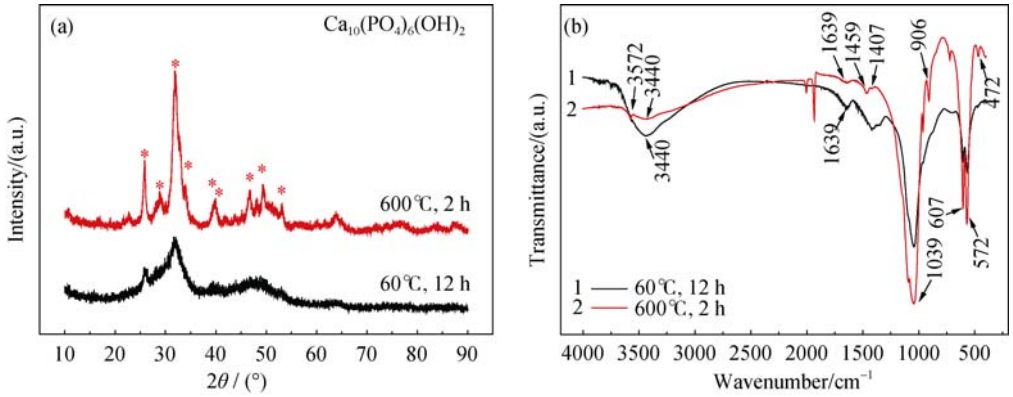

Fig. 4 XRD patterns (a) and FTIR spectrum (b) of the microspheres treated at different temperatures

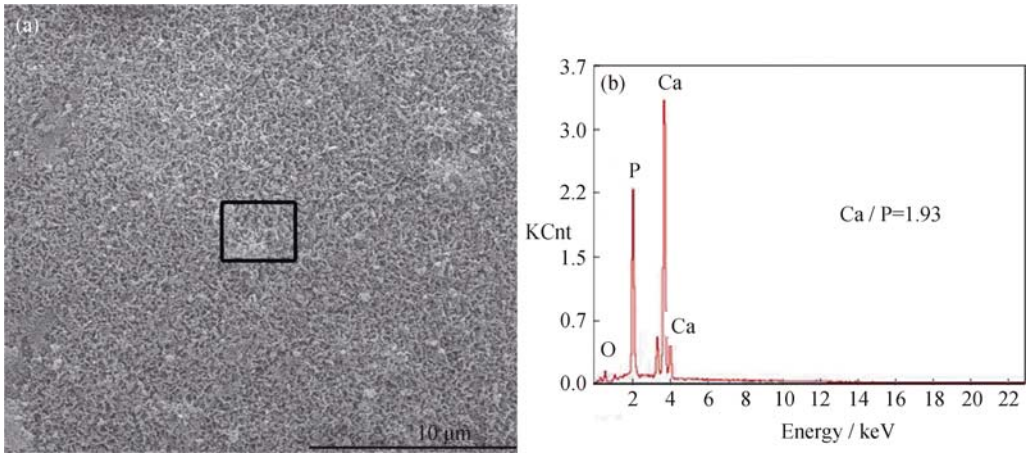

Fig. 5 EDS spectrum of the shell wall of the hollow HA microspheres
(a) Select location (black frame) of the EDS; (b) EDS spectrum

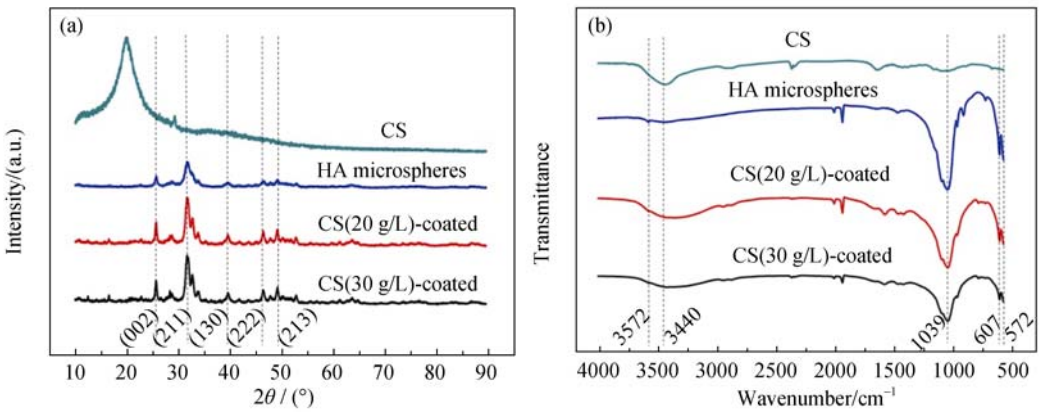

Fig. 6　XRD patterns (a) and FTIR spectra (b) of the CS-coated composite drug carrier

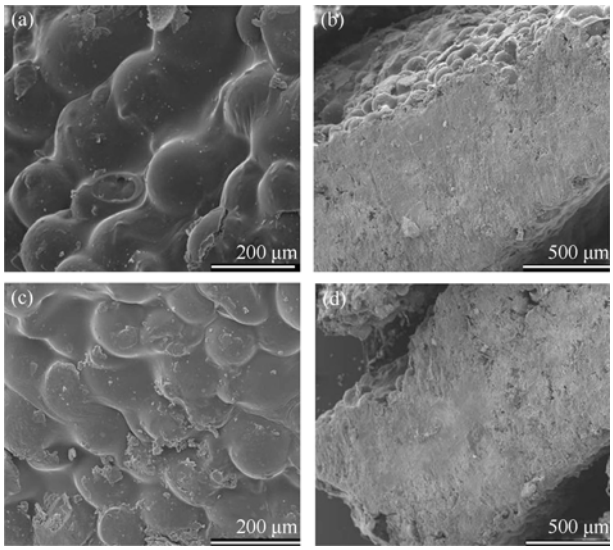

Fig. 7　SEM images of the surface and the cross-section of the CS-coated composite drug carrier

(a) Surface of the CS (20 g/L)-coated; (b) Cross-section of the CS (20 g/L)-coated; (c) Surface of the CS (30 g/L)-coated; (d) Cross-section of the CS (30 g/L)-coated

concentration of chitosan solution will lead to different coating thickness and further affect the drug release process. The flat and compact cross-section of the aggregates incised by the blade indicated that the microspheres was closely packed inside of composite aggregates and can be used in bone graft substitutes.

2.3　Drug release behavior *in vitro*

The average cumulative amount of vancomycin released into PBS with pH 7.4 at any time decreased with increasing the concentration of the CS coating solution, as shown in Fig. 8. The cumulative release percentage of the uncoated microspheres reached 39% at the initial stage and showed an initial ‘‘burst’’ release. The drug loaded on the surface of the shell wall released quickly due to the dissolve effect of PBS and the porous shell wall contributed to this phenomenon. Comparatively, after coating with CS, the release of vancomycin into PBS shows obvious delay.

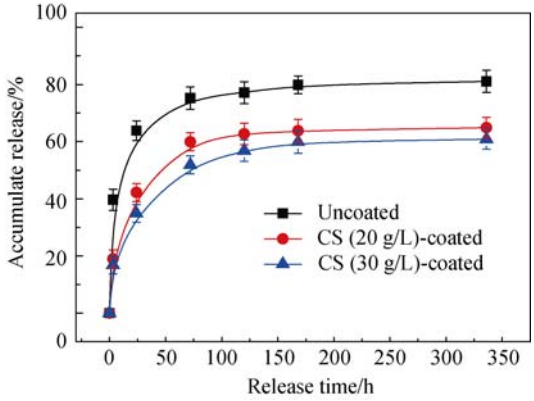

Fig. 8　The cumulative release percentage of vancomycin from the hollow HA microspheres, CS (20 g/L)-coated and CS (30 g/L)-coated composite drug carrier into PBS as a function of time

When the release experiments were terminated after 14 d, the cumulative release percentage of vancomycin into PBS was 81.09%, 64.91% and 60.85%, respectively, for the uncoated hollow HA microspheres, the CS (20 g/L)-coated and the CS (30 g/L)-coated composite drug carrier.

Base on the above results, although there is a certain degree of ‘‘burst’’ release, the release of vancomycin from the hollow HA microspheres into PBS were relatively slowly and continuously in the whole release process. The unique structural features of the hollow HA microspheres possibly contributed to this result, such as the high specific surface area and mesoporous shell wall. The desorbed drug could be readily re-adsorbed owing to the large amount of the HA surface area remain available for adsorption, which will markedly reduce the amount of the drug released into PBS[21]. Meanwhile, the tortuous mesopores of the shell wall (Fig. 2(b)) can make the release of vancomycin from the hollow core or the mesopores to the external surface difficult.

By using chitosan as the coating layer, the release rate of vancomycin from the hollow HA microspheres was significantly modified. Chitosan solutions with concentra-

tions of 20 g/L and 30 g/L were used to control the amount of the chitosan adhered on the microspheres. As the chitosan completely blocks the pores of the shell wall (Fig. 2), the initial release of the wall-adsorbed vancomycin into PBS was impeded. Thereafter, under the action of β-glycerophosphate, the chitosan coated layer produce gelation. This is because the hydrophobic force and hydrogen bond force is greater than the electrostatic repulsion between the chitosan molecular chains caused by the deprotonation effect, which increased the resistance of the drug release[22]. The thickness of the gel layer increased with increasing chitosan solution concentration, which increases the drug release resistance. The results showed that it is feasible to coat the hollow HA microspheres with chitosan to control the drug release property. Meanwhile, it is expected that optimization of the coating thickness depends on the clinical application. For instance, the use of a much higher drug dose requires the coating thickness to be adjusted accordingly in order to achieve optimum control on the release property[21].

2.4 pH-sensitive release behavior *in vitro*

The cumulative release percentage of vancomycin from the uncoated microspheres and the CS-coated composite drug carrier into PBS (pH=6.0, 7.4 and 8.5) as a function of time were shown in Fig. 9(a), (b) and (c). The release profile of vancomycin from the uncoated microspheres revealed that the drug release depends slightly on the pH of PBS (Fig. 9(a)). The cumulative release percentage into PBS at the release time of 80 h reached 84.04%, 85.04% and 87.84%, respectively for pH 8.5, 7.4 and 6.0, which shows no significant difference. The slightly higher release rate and cumulative release percentage of vancomycin at higher pH is due to the binding force between the vancomycin and the hollow HA microspheres. Higher pH of PBS lead to the weaker binding force and increase the drug release, as the isoelectric point of vancomycin is around pH 5.0[16].

In comparison, The CS (20 g/L)-coated composite drug carrier showed a significant pH-sensitive release profile (Fig. 9(b)). The cumulative release percentage of vancomycin in PBS with pH 6.0 was higher and comparable to that in PBS with pH 7.4 and 8.5 at any release time, and reached 85.63% when the release experiments were terminated after 14 d. In contrary, the accumulative release percentage in PBS with pH 7.4 was higher before the release time of 75 h and lower thereafter compared to that in PBS with pH value of 8.5, which reached 65.85% and 71.85% respectively when release terminated. The binding force between the vancomycin and the HA as mentioned before become weaker because of the higher pH (8.5) of PBS, which has played an important role during the later drug release process owing to the degradation of chitosan. The release profile of the CS (30 g/L)-coated carrier in PBS with different pH is similar to the CS (20 g/L)-coated carrier (Fig. 9(c)). The accumulate release percentage of it were lower than that of the CS (20 g/L)-coated composite drug carrier, reaching 80.12%, 60.85%, and 61.74% respectively for pH 6.0, 7.4 and 8.5.

The protonation effect and the Sol-Gel transition of chitosan might have contributed to the pH-sensitive release profile. Fig. 10 is the physical photo of the CS (20 g/L)- coated composite drug carrier at special time points immersing in PBS with different pH. The chitosan coating layer swelled into solution gradually with the extension of immersion time in PBS at lower pH 6.0 (Fig. 10). It is because that the hydrophobic force and hydrogen bond force less than the electrostatic repulsion between the chitosan molecular chains caused by the protonation effect at lower pH 6.0 and improves the drug release rate and cumulative release amount at the same time. In contrary, at the higher pH 7.4 or 8.5 of PBS, as shown in Fig.10, the chitosan coating layer produces gelation because of the hydrophobic force and hydrogen bond force greater than the electrostatic repulsion between the chitosan molecular chains caused by the deprotonation effect, which increases the resistance of the drug release[23-24].

SEM image of the composite drug carrier that was freezing-dried after immersing in PBS with the high pH 8.5 is shown in Fig. 11, in which some as-prepared hollow HA microspheres and the chitosan gel are visible. The results

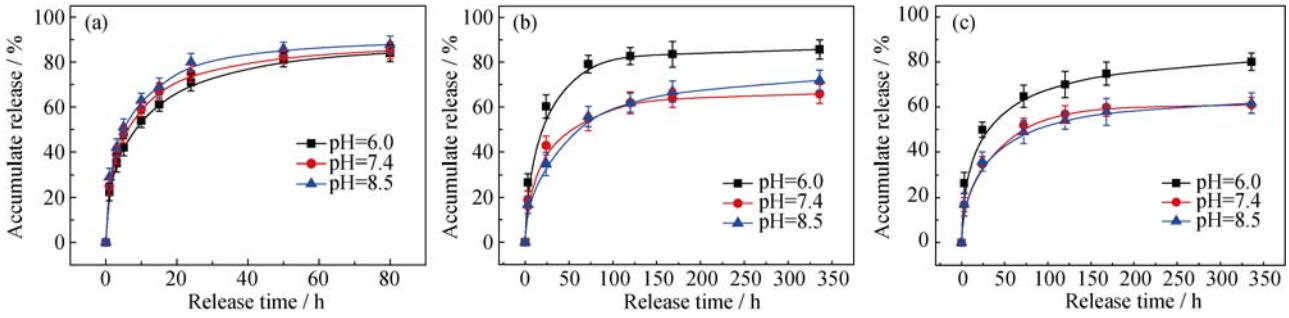

Fig. 9 The cumulative release percentage of vancomycin into PBS with different pH from the hollow HA microspheres (a), the CS (20 g/L)-coated composite drug carrier (b) and the CS (30 g/L)-coated composite drug carrier (c)

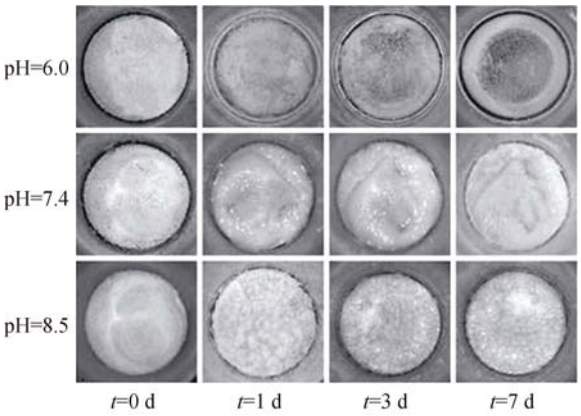

Fig. 10　Physical photos of the CS (20 g/L)-coated composite drug carrier at special time points immersing in PBS with different pH

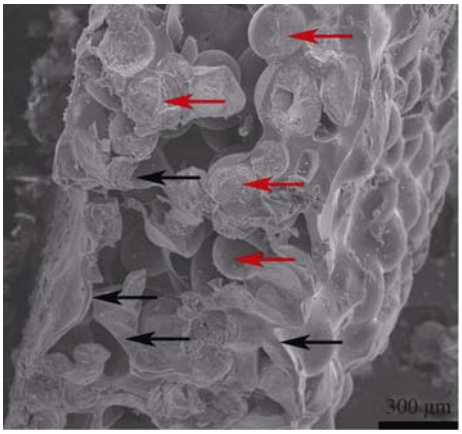

Fig. 11　SEM image of the CS (20 g/L)-coated HA microspheres after immersing in PBS with the high pH 8.5. Red arrows indicate the hollow HA microspheres; black arrows indicate the chitosan gel

showed that the CS-coated composite drug carrier may be used to control the drug release process as the change of pH value in bone diseases.

3　Conclusions

A novel hollow hydroxyapatite (HA) microspheres with mesopores on their surface were prepared by converting borate glass microspheres with a composition of $19Na_2O$-17CaO-$64B_2O_3$(wt%). The release of vancomycin from the HA microspheres occurred rapidly with a burst release at initial stage. Coating the HA microspheres with chitosan can significantly reduce the release amount. The release profile of vancomycin into PBS with different pH indicate that the CS-coated composite drug carrier have a pH-sensitive release property. The cumulative release percentage of CS (20 g/L)-coated composite drug carrier into PBS was 85.63%, 65.85% and 71.85% for pH 6.0, 7.4, 8.5, respectively. The results indicate that the novel composite drug carrier has a great potential application in bone repair.

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新型中空羟基磷灰石微球/壳聚糖复合药物载体用于药物控制释放

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摘 要: 利用中空羟基磷灰石微球和pH敏感型壳聚糖溶液制备了一种具有良好药物缓释和pH敏感型特性的新型复合药物载体材料。采用组分为 $19Na_2O$-17CaO-$64B_2O_3$(wt%)的硼酸盐玻璃在磷酸盐溶液中的原位转化反应制备了多壳层介孔中空 HA 微球, 通过 SEM、SEM-EDS、XRD 和 FTIR 等方法对产物微球进行表征。结果表明: 微球具有多层介孔中空结构, 且属于 B 型碳酸 HA。释药结果表明: 中空 HA 微球在释药初期产生了突释现象, 包覆壳聚糖后, 复合载体的释药量和释药速率显著下降。与此同时, 复合药物载体在不同 pH 的 PBS 溶液中表现出 pH 敏感型药物释放特征, 利用浓度 20 g/L 的壳聚糖溶液包覆的复合载体在 pH 为 6.0、7.4 和 8.5 的 PBS 溶液中的药物累积释放率分别为 85.63%、65.85%和 71.85%。

关 键 词: 中空羟基磷灰石(HA)微球; 复合药物载体; pH 敏感; 壳聚糖

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