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Hydroxyapatite Nanowhiskers Embedded in Chondroitin Sulfate Microspheres for Controlled Release of Terbinafine

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Introduction

Hydroxyapatite nanoparticles (n-HA) have important features that make it useful as adsorbent, such as its biomimetic morphologies, then, HA can be explored in drug delivery systems (DDS)[1]. Inorganic/organic hybrid materials can lead to highly disperse n-HA. Chondroitin sulfate (CS) is a natural polymer and it has intrinsic biocompatibility and biodegradability, and therefore a potential material for biomedical applications[2]. Terbinafine (TB) have been used for the treatment of distal lateral onychomycosis[3]. Our aim in the present study was to develop a DDS for TB delivery carrier. For this purpose, n-HA coated with CS microspheres were prepared with a series of n-HA contents (1%, 3%, 5%, 7% and 10 %) using the water in benzyl alcohol (W/O) microemulsion method.

Results and Discussions

The synthesis of n-HA was carried out by a wet chemistry method using $Ca(OH)_2$ and H_3PO_4. The n-HA synthesis was confirmed by FTIR, WAXR, BET, BJH and TEM. FTIR spectrum of as synthesized n-HA is shown in **Figure 1(a)**, where the main band is observed in 3569 cm^{-1}, characteristic stretching mode of OH groups. The n-HA particles observed in **Figure 1(b)** have structures akin to needles, also known as nanowhiskers. The pore diameter of the n-HA calculated by BJH method was c.a. 31 nm, which characterizes n-HA as a mesoporous material. The encapsulation efficiency of TB in n-HA was 77.5%, (c.a. 40.6 mg of TB per gram of n-HA).

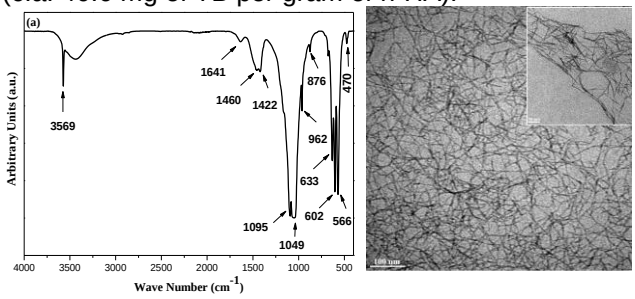

Figura 1. FTIR spectrum (a) and TEM (b) of n-HA.

The reaction mechanisms of CS with glycidyl methacrylate (CS-MET) have been reported by Reis et al[4]. The polymerization of CS-MET and the incorporation of n-HA (n-HA-CS microspheres) were performed by ultrasound using the methodology of microemulsion and characterized by ^{13}C-CP/MAS NMR and by FTIR, respectively, **Figure 2**. In the **Figure 2(I) (c)** it is observe the appearance of two signals at 40.9 and 32.8 ppm (CH_2-C) and the absence of signals at 141-120 ppm (C=C) which indicates the complete polymerization of CS-MET. In the FTIR spectrum it is observe the bands relating n-HA in the region of 1040, 602 and 566 cm^{-1} characteristic of stretch the P-O bond.

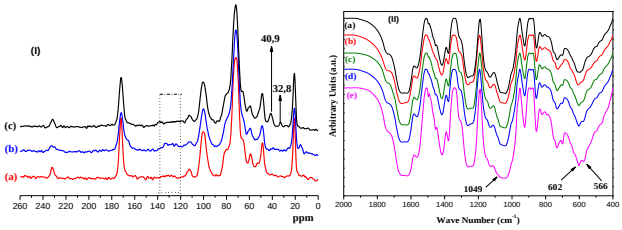

Figure 2: (I) ^{13}C-CP/MAS NMR spectra of CS (a), CS-MET (b) and n-HA-CS microspheres (c). (II) FTIR spectra for n-HA-CS microspheres containing 1% (a), 3% (b) 5% (c) 7% (d) and 10% (e) of n-HA.

The n-HA-CS microspheres was morphologically characterized by SEM and TEM, **Figure 3**. HA nanowhiskers are well distributed inside microspheres, indicating an excellent dispersion of n-HA if compared to the initial particles, that easily tend to form aggregates.

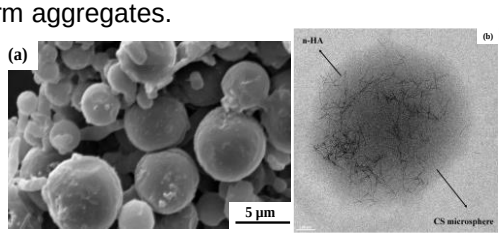

Figure 3. SEM images (a) and TEM images (b) of n-HA-CS microspheres containing 10% of n-HA.

The release profile of TB were evaluated by curves correlating the fraction of TB released in function of time. The mass percentage of TB released in simulated gastric fluid in equilibrium was c.a. 91.0% and in the simulated intestinal fluid c.a. 73.0%

Conclusions

n-HA were successfully synthesized obtaining nanowhiskers with crystallite size of 8.41 nm showing effective adsorption of TB, c.a.77%. The synthesis of n-HA-CS microspheres via ultrasound proved to be an efficient and novel method to date in both crosslinking and formation of spherical particles. The releasing of TB is very interesting, because occurred in both simulated fluid, then after remaining in the stomach, the microspheres may continue releasing the drug in other physiological environment, since a CS degrades only in the colon by anaerobic bacteria.

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