Synthesis of water-dispersible silicon-containing hydroxyapatite nanoparticles with adjustable degradation rates and their applications as pH-responsive drug carriers

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Silicon-containing hydroxyapatite (Si–HAp) nanoparticles with adjustable degradation rates were successfully synthesized via simple hydrothermal treatment of a precursor, calcium silicate hydrate powder, in trisodium phosphate aqueous solution. The degradation rate of the products could be facilely tailored by regulating the hydrothermal temperature, while the obtained Si–HAp nanoparticles exhibited high loading capacities toward doxorubicin (DOX) as well as sustained and pH-dependent drug release properties. HeLa cell culture results confirmed that the toxicity of DOX loaded in Si–HAp nanoparticles was more sustained than that of free DOX. Their biodegradability, good water dispersibility and drug-loading capacity, and sustained and pH-responsive drug release properties suggest that these synthetic Si–HAp nanoparticles have great potential applications as drug carriers.

1 Introduction

Because of their excellent bioactivity and biocompatibility, hydroxyapatite [Ca_{10}(PO_4)_6(OH)_2, HAp] nanomaterials not only offer favorable environments for osteoconduction and bone ingrowth, protein/drug loading and delivery systems, but also play a significant role in maintaining the mechanical properties of natural bone.1–3 Well-dispersed HAp nanoparticles can contribute to the processes of biomaterial composite systems to improve their mechanical properties, and may also enhance bone healing and remodeling interactions.4 Moreover, well-dispersed HAp nanoparticles are also important in drug delivery and electrophoretic deposition.

However, one of the most challenging issues for the use of nanoparticles as drug carriers is their tendency toward agglomeration. To date, several strategies have been developed to solve this problem. Mechanical stirring,5 ultrasound treatment,6 chemical techniques,7,8,9,10 etc. have been widely used to reduce agglomerate formation and improve dispersion to a certain extent during solution processing of HAp particles. Unfortunately, mechanical stirring and ultrasound treatment are temporary; particle agglomeration will reoccur once the mechanical energy or the ultrasound energy is removed. Chemical techniques can provide more permanent solutions to the issue of HAp dispersity. Li et al.6 exploited the existence of electrostatic repulsions between the particles to achieve high dispersibility of HAp–PEO–NaO1 in aqueous solution. In addition, special organic ion or molecule modification methods such as citrate,7 silane coupling,8 pyrophosphoric acid,9 dodecyl alcohol10 and silk fibroin11 have been developed to maintain good dispersion of HAp nanoparticles. However, the abovementioned methods require the use of large amounts of additional organic reagents, which may be detrimental to health during use in biomedical applications.

In addition to dispersity, degradation behavior is another important issue for drug carriers. It is well known that mesoporous silica can be a useful and controllable drug delivery carrier due to its high specific surface area, well-ordered mesoporous structure and large pore volume.12 However, the poor degradability of silica limits its bio-applications because the insoluble portions of the silica matrix may accumulate in vivo.12 The degradability of stoichiometric HAp particles is very poor, which severely hinders their wider applications in drug carriers. There have been many attempts to improve the degradability of HAp by decreasing its crystallinity13 and incorporating degradable materials, such as β-tricalcium phosphate,14 glass15 and polymers.16 Another approach to improve the degradation rate of HAp is doping essential trace elements into the HAp crystal sites.17,18 Previous studies have suggested that essential trace element doping results in lower crystallinity and the distortion of crystal structures, which leads to higher degradation rates.17,18
To date, the hydrothermal method has been considered to be a facile approach to synthesize single crystalline HAp particles. After hydrothermal treatment of the HAp precipitates in aqueous solution obtained by chemical precipitation, HAp nanoparticles with high crystallinity can be easily prepared. However, the powders obtained via this method usually demonstrate severe agglomeration, and the size distribution is usually in a wide range. The hydrothermal-microemulsion technique was successfully developed to synthesize HAp nanoparticles with monodispersion and narrow size distribution. In this technique, nucleation and crystal growth can be well restricted in uniform nano-reactors formed in the microemulsion system. However, the formation of a microemulsion requires large amounts of organic template and solvents, which are harmful to health and the environment. In addition, it is difficult to synthesize materials on a large scale using hydrothermal-microemulsion technology.

Recently, we developed a facile, environmentally friendly hydrothermal transformation method to synthesize HAp materials with controllable morphologies and chemical compositions using calcium silicates as precursors. In the present study, the hydrothermal transformation of calcium silicate hydrate (CHS) precursor in trisodium phosphate aqueous solution, without the use of any surfactants, template-directed reagents or organic solvents, was applied to synthesize water-dispersible silicon-containing hydroxyapatite (Si-HAp) nanoparticles with adjustable degradation rates. Then, the drug loading and release of the obtained products were investigated, and the cytotoxic activities of doxorubicin-loaded nanoparticles were analyzed in vitro against HeLa cells. To date, studies have revealed that the incorporation of Si element into the lattices of HAp can noticeably improve the biological properties of the products. These studies suggest that the Si components released from Si-HAp materials can stimulate the proliferation and osteogenic differentiation of osteoblasts and bone mesenchymal stem cells, thereby improving osteogenic induction ability. Several methods, including the coprecipitation route, hydrothermal method, and sol–gel approach, have been developed to synthesize Si-HAp nanoparticles. However, it is still difficult to obtain Si-HAp nanoparticles with water dispersibility and narrow size distribution on a large scale using these traditional synthetic methods.

2 Materials and methods

All the chemicals and reagents (Shanghai Chemical Co., Ltd., China) used in this study for the synthesis of Si-HAp nanoparticles were of analytical grade and were used without further purification.

2.1 Synthesis of water dispersible Si-HAp nanoparticles

The calcium silicate hydrate (CASH) powder precursor was prepared by a chemical precipitation method. Briefly, an aqueous solution of 0.5 M Ca(NO₃)₂ and an aqueous solution of 0.5 M Na₂SiO₃ were prepared by dissolving reagent grade Ca(NO₃)₂·4H₂O and Na₂SiO₃·9H₂O in deionized water, respectively. The molar ratio of Ca²⁺ and SiO₃²⁻ was set at 1.0. The Ca(NO₃)₂ solution was added dropwise to the Na₂SiO₃ solution under vigorous stirring to produce a white suspension. After the addition was complete, the white precipitate was further stirred for 24 h, and then washed three times with deionized water and one time with absolute ethyl alcohol. After washing, the remaining liquid was removed by vacuum filtration. Finally, the obtained powders were dried at 120 °C for 24 h.

The obtained CSH powders were used as the precursors to synthesize water dispersible Si-HAp nanoparticles. Briefly, 2 g CSH powder was mixed with 85 mL 0.4 M Na₃PO₄ aqueous solution in a polytetrafluoroethylene vessel. Then, the vessel was sealed in a stainless steel autoclave and heated at 120 °C, 150 °C and 180 °C for 24 h. After hydrothermal treatment, the reaction system was cooled to room temperature. The products were washed and filtrated as described above and dried at 120 °C for 24 h.

2.2 Characterization

The morphologies, sizes and aspect ratios of the obtained products were observed by transmission electron microscopy (TEM: JEM-2100F, JEOL, Japan). The chemical compositions of the products were tested by inductively coupled plasma atomic emission spectroscopy (ICP-AES; 715-ES, VISTA AX, Varian Co., USA). In this technique, 0.03150 g Si-HAp nanoparticles were dissolved in 1 : 1 hydrochloric solution and diluted to a final volume of 250 mL. The final solutions were used as the determination solutions. Stock solutions containing 0, 1, 20 and 50 μg mL⁻¹ of Ca, P and Si were used as standards for the preparation of calibration curves. All standard reagents were guaranteed grade, and the standard solutions were prepared with Milli-Q water (18 MΩ cm). The surface area of the products was measured on a Micromeritics Tristar 3000 system. The zeta potentials of the synthetic products were determined with a zeta potential measurement analyzer (ZetaPlus, Brookhaven, USA) in physiological saline (0.154 M NaCl solution) at pH 7.4. The products were characterized with X-ray diffraction (XRD: D/mx 2550V, Rigaku, Japan) with monochromated Cu-Kα radiation and Fourier transform infrared spectroscopy (FTIR: Nicolet Co., USA). The crystallinity degree (Xc) of the products was evaluated by following equation:

\[ X_c = \left[ 1 - \frac{V_{112/300}}{I_{300}} \right] \]

where \(I_{300}\) is the intensity of the (3 0 0) reflection and \(V_{112/300}\) is the intensity of the hollow between the (1 1 2) and (3 0 0) reflections.

2.3 In vitro studies of the degradability of the Si-HAp nanoparticles

The in vitro degradability of the obtained Si-HAp nanoparticles was evaluated by examining the weight loss percentages of the products in Tris–HCl buffer solution. The 0.1 M Tris–HCl buffer solution was prepared by dissolving analytical reagent grade tris(hydroxymethyl) aminomethane in distilled water; the solution was then adjusted to pH 7.4 at 37 °C with 1 M hydrochloric acid aqueous solution. The synthetic Si-HAp
nanoparticles were soaked in Tris–HCl buffer solution at 37 °C in a shaking water bath for 7 days at a solid/liquid ratio of 1.50 mg mL\(^{-1}\) without refreshing the soaking medium. After soaking, the samples were centrifuged and the supernatant solution was applied to examine the released ions by ICP-AES.

Based on the fact that no Ca was present in the Tris–HCl buffer solution, the dissolution ratio (S) of the powders was calculated according to the following equation:

\[
S = \left( \frac{C_{Ca} \times V}{m_{Ca}} \right) \times 100\%
\]

where \(C_{Ca}\), \(V\) and \(m_{Ca}\) are the Ca concentration in Tris–HCl (mg mL\(^{-1}\)), the volume of Tris–HCl (mL) and the Ca content (mg) of the samples soaked in Tris–HCl, respectively.\(^{17}\)

2.4 In vitro study of drug loading and release properties

The anti-cancer drug doxorubicin (DOX) model was used to determine the drug loading and release properties of the synthetic Si-HAp nanoparticles. The DOX powders were purchased from Aladdin. 5 mg of the obtained Si-HAp nanoparticles was mixed with 1 mL of DOX aqueous solution (1 mg mL\(^{-1}\)). The mixture was incubated at 37 °C in a shaking air bath for 24 h in the dark because DOX is sensitive to photolytic decomposition. Drug-loaded samples were separated from unbound drug molecules by centrifugation at 8000 rpm for 5 min. After that, the samples were carefully washed three times with 1 mL of distilled water to remove the physically adsorbed drug molecules. The DOX loading capacity was measured using UV/Vis spectroscopy with a microplate reader (BioTek Instruments, USA) at a wavelength of 480 nm. A calibration curve (correlation coefficient \(R^2 = 0.9999\)) was made for each set of measurements and determined by taking the absorbance \(A\) vs. the DOX concentration between 0 and 125 \(\mu\)g mL\(^{-1}\) as parameters. The drug loading capacity was calculated according to the following formula:

\[
\text{DOX loading capacity} = \left( \frac{A - B}{C} \right) \times 100\%
\]

where \(A\), \(B\) and \(C\) represent the amounts of the initial drug, the final drug and the powder, respectively.

Drug release from the Si-HAp nanoparticles was analyzed both at physiological pH (7.4) and at acidic pH (5.0). The DOX-loaded Si-HAp nanoparticles (5 mg) were placed in 2 mL of phosphate buffer solution (PBS) at pH 7.4 or at pH 5.0 and agitated in a shaking air bath at 37 °C for 1 h, 3 h, 6 h, 9 h, 24 h, 2 d, 3 d, 5 d and 7 d. At the predetermined time intervals, the solutions were centrifuged, and then the release medium was withdrawn and replaced with fresh release medium (1 mL). The amount of drug release was measured by UV/Vis spectroscopy.

2.5 Cytotoxicity assays for the Si-HAp nanoparticles

The cell toxicity was determined using the Cell Counting Kit-8 (CCK-8, Beyotime, China) assay according to the manufacturer’s instructions. HeLa cells were plated at a density of 5000 cells per well in a 96-well plate and incubated in 100 \(\mu\)L cell culture medium at 37 °C in 5% CO\(_2\) atmosphere for 12 h.

Table 1. Details of the concentrations of Si-HAp, DOX and DOX-loaded Si-HAp nanoparticles in the cytotoxicity assay

<table>
<thead>
<tr>
<th>Sample</th>
<th>(c_1) ((\mu)g mL(^{-1}))</th>
<th>(c_2) ((\mu)g mL(^{-1}))</th>
<th>(c_3) ((\mu)g mL(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Si-HAp nanoparticles</td>
<td>12.5</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>Free DOX</td>
<td>1.25</td>
<td>2.5</td>
<td>5</td>
</tr>
<tr>
<td>DOX-loaded Si-HAp nanoparticles(^a)</td>
<td>13.75</td>
<td>27.5</td>
<td>55</td>
</tr>
</tbody>
</table>

\(^a\) The drug loading amount on the Si-HAp nanoparticles was similar to that in free DOX solution.

Subsequently, the medium was removed and replaced by culture medium containing DOX, Si-HAp or DOX-loaded Si-HAp nanoparticles with different concentrations (Table 1). After 24 h, 48 h or 72 h of further incubation, the 100 \(\mu\)L CCK-8 solution (diluted 10 times with cell culture medium) was added to each well and incubated for a further 1 h at 37 °C, 5% CO\(_2\). The absorbance was then measured at 450 nm using a microplate reader (BioTek Instruments, USA.). All experiments were performed in triplicate.

3 Results and discussion

3.1 Characterization of the Si-HAp nanoparticles

Fig. 1 shows the morphology and size of the nanoparticles obtained by hydrothermal transformation of CSH in trisodium phosphate aqueous solution at different temperatures for 24 h. The TEM images confirmed that the obtained products were rod-like in shape and nano-sized; in addition, the size of the particles increased with increasing hydrothermal transformation temperature. In addition, the digital photographs confirm that the obtained products possess excellent dispersibility, which may prevent severe agglomeration in biomedical applications and is beneficial to the applications of the particles as drug carriers. The average lengths, widths and aspect ratios of the nanoparticles synthesized at different temperatures are further summarized in Table 2. The results further confirmed that the average length, width and aspect ratio increased from 36.76 to 79.50 nm, 12.61 to 19.04 nm, and 2.9 to 4.2, respectively, as the hydrothermal transformation temperature increased from 120 °C to 180 °C. In addition, the synthetic Si-HAp nanoparticles possess negative zeta potential,
as characterized in physiological saline at pH 7.4. The average zeta potentials of the hydrothermal transformation products from CSH at 120 °C, 150 °C and 180 °C were −3.94, −4.56 and −4.94, respectively. Previous studies suggest that the negative zeta potentials of HAp materials may be advantageous for their applications in viable cell delivery systems or bone grafts.\textsuperscript{31,32} Moreover, the presence of negative surface charges is conducive to the binding of DOX drugs with positive charges.\textsuperscript{33}

Fig. 2 shows the XRD patterns of the products synthesized under different conditions. The results indicate that all of the obtained nanoparticles could be identified as pure HAp phase (JCPDS card: no. 09-0432). The increase of the hydrothermal transformation temperature resulted in an increase of the crystallinity because a higher hydrothermal temperature is beneficial to the crystal growth of HAp. The crystallinity values calculated from the XRD determination results further confirmed that the crystallinity ($X_c$) increased from 0.3551 to 0.5407 and 0.5581 when the hydrothermal transformation temperature was increased from 120 °C to 150 °C and 180 °C, respectively (Table 2).

The FTIR spectra of the Si-HAp nanoparticles synthesized under different hydrothermal transformation temperatures are presented in Fig. 3. The bands that appeared in the spectra are in good agreement with the reported FTIR data for HAp. The peaks present at around 471, 563, 602, 956, 1031 and 1096 cm\textsuperscript{-1} are the characteristic bands of $\text{PO}_4^{3-}$.\textsuperscript{17} The bands at around 1456, 1415 and 879 cm\textsuperscript{-1} are attributed to the $\text{CO}_3^{2-}$ group; these may arise from the $\text{CO}_2$ dissolved in aqueous solution.\textsuperscript{17} The peaks around 1641 and 3438 cm\textsuperscript{-1} were assigned to the

| Table 2 | Size, chemical composition, crystallinity and zeta potential of the Si-HAp nanoparticles synthesized under various hydrothermal conditions |
|-----------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Hydrothermal conditions            | Average length (nm) | Average width (nm) | Average aspect ratio | Si content (wt%) | Ca/(P + Si) molar ratio | Zeta potential (mV) in physiological saline with pH = 7.4 | Crystallinity ($X_c$) |
|-----------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------
| 120 °C/24 h                        | 36.76           | 12.61           | 2.9             | 0.51 ± 0.04     | 1.67            | −3.94 ± 1.65    | 0.3551          |
| 150 °C/24 h                        | 50.27           | 15.48           | 3.4             | 0.53 ± 0.01     | 1.66            | −4.56 ± 0.93    | 0.5407          |
| 180 °C/24 h                        | 79.50           | 19.04           | 4.2             | 0.55 ± 0.02     | 1.65            | −4.94 ± 1.18    | 0.5581          |
bending mode of the absorbed water.\textsuperscript{17} Compared with classical pure HAp materials, the characteristic OH band of HAp that appeared at approximately 3568 cm\textsuperscript{-1} was very weak, and that at 634 cm\textsuperscript{-1} almost disappeared in Fig. 3 due to the substitution of the PO\textsubscript{4} group by SiO\textsubscript{4}.\textsuperscript{23} The FTIR result further confirmed that the products from hydrothermally transformed CSH were silicon substituted hydroxyapatite (Si-HAp) materials, and the positions of the peaks were not affected by Si substitution.

### 3.2 The degradability of Si-HAp nanoparticles in vitro

Adjustable degradability is an important requirement for the wider biomedical applications of HAp materials. Fig. 4 shows the quantitative dissolution rates of the synthetic Si-HAp nanoparticles after soaking in Tris-HCl buffer solution for 7 days. The weight losses of the Si-HAp nanoparticles synthesized at 120 °C, 150 °C and 180 °C were 2.2, 1.5 and 1.2 wt%, respectively. When the hydrothermal transformation temperature decreased from 180 °C to 120 °C, the degradation rate increased to around 83%, which was attributed to the decrease of the crystallinity of the products synthesized at lower hydrothermal transformation temperatures.\textsuperscript{17,18}

### 3.3 The DOX loading and release properties of Si-HAp nanoparticles in vitro

HAp materials have been widely used as drug loading and delivery systems.\textsuperscript{17} In the present study, the drug loading and release properties of the synthetic Si-HAp nanoparticles were further investigated using DOX as a model. The amounts of loaded DOX for the synthetic Si-HAp nanoparticles are shown in Table 3. The sample synthesized at 120 °C showed the highest loading capacity, which was due to the highest specific surface area (S\textsubscript{BET}) of the samples at the lowest hydrothermal treatment temperature (Table 3). It is well known that the drug loading amount (DLA) is greatly related to the intrinsic nature of the carrier material and the molecular structure of the loaded drug. The –OH functional groups in HAp materials have strong affinities towards the –OH and –NH\textsubscript{2} groups of the DOX molecules through H-bond interactions. Therefore, the sample with higher S\textsubscript{BET} provided many more active sites to quickly adsorb higher amounts of DOX.

Fig. 5A presents the cumulative release results of DOX from the Si-HAp nanoparticles from hydrothermally transformed CSH precursors in trisodium solution at different temperatures in PBS. It is clear that DOX showed similar release behavior during the entire period; an evident two-step release behavior was observed, with an initial fast release and a relatively slow subsequent release. However, the drug release rate of the sample synthesized at 120 °C was significantly lower than those synthesized at 150 °C and 180 °C. The initial burst release of the sample obtained at 120 °C within the first 9 h was around 4.13 wt% of the total amount of DOX in PBS at pH 7.4. The subsequent release rate decreased remarkably as the soaking time was prolonged; the cumulative release increased slowly over the next 7 days, reaching a maximum value of 8.66 wt% in PBS. Moreover, for the samples obtained at higher temperatures of 150 °C and 180 °C, the drug release rate was remarkably improved; around 7.5 wt% of the total loaded drug was released in the first 9 h, and after 7 days, the total amounts of released DOX reached 16.71 and 18.83 wt%, respectively. The lower release rate suggests stronger binding forces between the DOX molecules and the Si-HAp nanoparticles synthesized at 120 °C. However, the mechanisms behind these phenomena should be further investigated in detail. Moreover, the sample synthesized at 120 °C was selected for further investigation of its pH-responsive release properties.

### Table 3 The specific surface areas and DOX loading capacities of the Si-HAp nanoparticles from hydrothermally transformed CSH in trisodium phosphate aqueous solution at different temperatures

<table>
<thead>
<tr>
<th>Synthetic conditions</th>
<th>Specific surface area (m\textsuperscript{2} g\textsuperscript{-1})</th>
<th>DOX loading capacity (mg g\textsuperscript{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>120 °C/24 h</td>
<td>142.2</td>
<td>100.00</td>
</tr>
<tr>
<td>150 °C/24 h</td>
<td>118.5</td>
<td>51.30</td>
</tr>
<tr>
<td>180 °C/24 h</td>
<td>119.3</td>
<td>52.47</td>
</tr>
</tbody>
</table>

### Fig. 5 The cumulative release ratio of DOX from the Si-HAp nanoparticles synthesized at 120 °C, 150 °C and 180 °C, respectively in PBS with pH = 7.4 (A), and the in vitro pH-responsive DOX release behaviors of the Si-HAp nanoparticles synthesized at 120 °C in two different release media with pH values which were used to simulate the alkaline conditions in normal tissues and blood (pH ~ 7.4) and the acidic conditions in tumor tissues (pH < 6.8) (B).
Fig. 5B confirms that the release of DOX from the synthetic Si-HAp nanoparticles clearly depends on the pH value of the soaking medium. When the pH value of the medium was decreased from 7.4 to 5.0, the cumulative release amount of DOX from the carriers increased remarkably, from 14.04 to 25.04 wt% of the total drug loading amount. The total release ratio increased to about 78.34%; this was attributed to the increased dissolution of Si-HAp at the lower pH value of the acidic media. It is well known that HAp materials degrade slowly in physiological medium (pH ~ 7.4) and much faster in acidic medium. With the decrease of the pH value from alkaline to acidic conditions, the dissolution rate of Si-HAp increases significantly, which promotes the detachment of DOX drugs from the surfaces of the Si-HAp nanorod carriers. The results reveal that the release of DOX from the hydrothermal transformation-synthesized Si-HAp nanoparticles is greatly dependent on the local pH. Therefore, synthetic Si-HAp with controllable degradation rates may provide a new platform as a promising candidate in the formulation of the in vivo targeted delivery of therapeutic agents to tissues with low-pH environments, such as tumors and inflammatory sites.

The Si-HAp nanoparticles synthesized at 120 °C were selected as DOX carriers to study their effects on HeLa cells in vitro because they had the fastest degradation rate of the three synthetic conditions. The cytotoxicities of pure DOX, bare Si-HAp nanoparticles, and DOX loaded Si-HAp toward HeLa cells were evaluated using the standard CCK-8 assay. In this assay, the cytotoxicity was tested under three different concentrations (Table 1). As shown in Fig. 6, the cytotoxicity of the DOX-loaded Si-HAp nanoparticles was both dose- and time-dependent. After 24 h of culture, about 48.92% of the HeLa cells were killed at the highest concentration tested (e.g., 55 µg mL⁻¹; the loaded DOX was 5 µg mL⁻¹), and the inhibition ratio reached 97.8% at 72 h. However, the inhibition ratio of free DOX reached a high level of 77.2% after 24 h of culture at a drug concentration of 1.25 µg mL⁻¹ and then increased rapidly to 95.6% when the culture time was increased to 48 h (Fig. 5a). It is clear that the cytotoxicity of DOX loaded on the Si-HAp nanoparticles for HeLa cells is significantly lower than that of free DOX due to the gradual and partial release of DOX from the carriers. However, no cytotoxicity was observed toward HeLa cells for the bare Si-HAp nanoparticles at all three concentrations over the entire period, which illustrated that the cytotoxicity of DOX-loaded Si-HAp can be attributed to the release of DOX into the cells.

It is well known that free DOX is highly toxic to humans. Therefore, the use of Si-HAp nanoparticles as carriers and protectors is necessary to reduce premature release before arrival at the target sites. The present study suggests that there are several advantages to using the synthetic Si-HAp nanoparticles as drug carriers. First, the nanoparticles possess excellent water dispersibility, which is beneficial for their applications via intravenous administration. Second, the DOX loaded on the Si-HAp nanoparticles was more stable at pH = 7.4 than at pH = 5.0, which reduced the cytotoxicity to normal cells during circulation in the body. Third, the degradability of the carriers is beneficial for their removal from the body through dissolution in vivo. Particularly, the acidic conditions in tumor tissue can further accelerate the dissolution rate of the synthetic HAp materials. Furthermore, the degradation products of the carriers are calcium and phosphate ions, which are cytocompatible with human body tissues.

4 Conclusion

In summary, water-dispersible Si-substituted hydroxyapatite (Si-HAp) nanoparticles with adjustable degradation rates were successfully synthesized via hydrothermal treatment of calcium silicate hydrate powder in trisodium phosphate aqueous solution without using any surfactants, template-directed reagents or organic solvents. The degradation rate was strongly related to the crystallinity of the Si-HAp products and could be facilely regulated by the hydrothermal temperature. The synthetic Si-HAp nanorods showed high loading capacities toward DOX, and the release behavior of DOX was pH dependent. DOX was more easily released from the Si-HAp nanoparticles in acidic media. The cytotoxicity of the DOX-loaded Si-HAp particles against HeLa cells was more permanent than that of free DOX. The degradability and highly pH-dependent loading and release properties of the DOX-loaded Si-HAp nanoparticles endure them with promise as a strategy to enhance the efficiency of anti-tumor therapy.
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Notes and references