In situ assembly of Mt-HAP drug carrier with pH-responsive sustained release properties

Shaohui Wang, Bo Wen, Congying Xie, Meiling Zhong, Yongxin Liu, Zanru Guo and Jiali Zhang

School of Materials Science and Engineering, East China Jiaotong University, Nanchang 330013, People’s Republic of China

E-mail: shhwang2008@sina.com

Keywords: amoxicillin, hydroxyapatite, montmorillonite, sustained release, pH-responsive

Supplementary material for this article is available online

Abstract

The Mt-HAP composites were achieved by combining layered montmorillonite (Mt) and hydroxyapatite (HAP) nanoparticles produced by in situ assembly technique. Amoxicillin (AMX) loading and release experiment proved that the synthetic Mt-HAP composites demonstrated high drug loading ability and pH-responsive sustained release property. The AMX load of original Mt was 18.5 mg g\(^{-1}\), while that of Mt-HAP grew to 49.1 mg g\(^{-1}\). Experiments in simulated gastric fluid (pH 1.2) release indicated that Mt drug carrier having a higher release rate of AMX within the initial 2 h. But after that, the drug release rate of AMX from Mt-HAP has a greater value (about 65% over 12 h) than that of Mt (about 50% over 12 h) because of the dissolution of HAP under acidic circumstance. However, the cumulative sustained release rate of Mt-HAP in simulated intestinal fluid (pH 6.8) over 12 h was only 30%, and the drug release amount of Mt was still about 49%. Compared to Mt@AMX, the drug release rate of Mt-HAP@AMX is sensitive to changes in pH. The findings claimed that the Mt-HAP composite exhibited extreme potential as a drug carrier for controllable drug delivery.

Introduction

About 17 million people die of bacterial infection per year, which is the 2nd main reason of human death [1]. The misuse of antibiotics and the formation of bacterial biofilms bring about the growing number of drug-resistant bacteria [2]. Amoxicillin (AMX) was widely used as a \(\beta\)-lactam antibiotics [3]. It can easily penetrate cell membranes and remain stable under acidic conditions. Due to its high antibacterial activity, it is used in the treatment of certain diseases [4]. As a result, AMX might be discovered in body fluids and animal tissues subjected to utilization of drugs [5]. However, as an alkaline drug, limited by its rapid dissolution rate in acid environment, a quick initial release can be discovered. Some lesions (e.g. cancer) require long-term medication, while oral AMX dissolves quickly under acidity in the stomach fluid, resulting in an excessive amount of drug accumulation in the body fluid locally. AMX overdose may lead to gastrointestinal discomfort, liver and kidney damage [6, 7]. Accordingly, it is urgent necessary to exploit an AMX drug loading system to solve the problem of oral administration in clinical applications [8].

Hydroxyapatite (HAP) \([\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2]\), as a main inorganic component of teeth and bones, approved by the food and drug administration (FDA) [9, 10]. Due to its excellent bioactivity, biocompatibility and biodegradability, HAP has been widely used in the field of biomedical materials, [11, 12]. Recently, various types of HAP based drug delivery systems have been developed through an enormous amount of studies [13]. However, although HAP as a drug carrier has a certain sustained-release effect, the problems of low drug loading and instability of the carrier in acidic media still exist [14]. Thus, the slow release can be realized by controlling the dissolution rate of HAP loaded particles in body fluids. The surface modification materials, such as chitosan, PE coating and so on, have been studied in order to reduce release rate of drugs [15, 16]. But there is no greater breakthrough in the adsorption capacity of drugs. Therefore, a simple and practical method is to use montmorillonite with high adsorption capacity as the protective carrier.
The montmorillonite (Mt) is one kind of natural minerals with the crystal structure of 2:1 layered silicate, which has been widely applied to pharmaceutical and other industrial fields based its particular properties, such as expansibility, dispersivity, ion exchangeability and absorbability [17, 18]. Not only that, it also proves all the differences of Mt certification with low toxicity through biochemical testing and tissue analysis. It has been employed in the cure for intestinal problems, stomach ulcers, diarrhea and other diseases [19].

Because of these distinguishing characteristics and various therapeutic effects, it has taken the credit to be named medical clay. Compared with other polymer carriers such as chitosan, the strong adsorption capacity of Mt makes it the preferred drug carrier. To obtain more outstanding loading capability and pH-responsive sustained drug release performance, an originality combination of layered Mt and HAP nanoparticles produced by in situ synthesis has been proposed.

In this work, the Mt-CaCO₃ and Mt-HAP composites were designed and synthesized, which has drug loading ability and pH-responsive sustained release performance. The properties of samples were characterized by Fourier transform infrared spectroscopy (FT-IR), x-ray diffraction (XRD), scanning electron microscopy (SEM), Thermogravimetric Analysis (TGA) and Brunauer–Emmett–Teller (BET). The aim is to find the law of drug release for loaded particles in simulated gastrointestinal fluid and examine the drug loading level and pH-responsive sustained release ability, in vitro release characteristics of the composites were carried out.

Materials and methods

Materials

Amoxicillin (AMX) was provided from Sigma-Aldrich (St. Louis, MO. American). Na-montmorillonite (Mt) with a CEC of 97 mmol/100 g was purchased from Zhejiang Fenghong new Material Co., Ltd (Huzhou, China). The chemical composition of Mt wt%: SiO₂ 66.78, Al₂O₃ 17.12, Fe₂O₃ 2.94, MgO 2.90, Na₂O 2.35, K₂O 1.62, TiO₂ 0.82, CaO 0.41. Other reagents and chemicals were of analytical grade and used in this study were purchased from the Sigma-Aldrich Trading Co., Ltd (Shanghai, China). All aqueous solutions were prepared using distilled water.

Preparation of Mt-CaCO₃ and Mt-HAP

The synthetic scheme of Mt-HAP by in situ assembly was described in figure 1. The first step is to add 150 ml of wt.1% MT suspension and 30 ml of 0.5 mol ml⁻¹ CaCl₂ solution into a 250 ml four port flask with round bottom. The resulting combination was agitated under normal temperature for 6 h and stand on the test bench for 12 h. Removed the supernatant fraction and washed repeatedly with distilled water until free of Ca²⁺ ion ((NH₄)₂C₂O₄ test) [20, 21]. The second step is to disperse the washed samples in the first step with 100 ml ethanol-water solution (50 ml:50 ml), the whole mixture was stirred for 12 h in an ice bath and slowly aerate with CO₂. The product of this stage was sampled, dried to constant weight and named as Mt-CaCO₃. The third step, 50 ml of 0.5 mol ¹⁻ NaH₂PO₄ solution was added into the suspension of the previous stage, then poured into a simple high-pressure reaction kettle of 500 ml (PTFE lining), and placed the reaction kettle in oven of 120 °C for 2 h. At the end of the reaction, the suspension was filtered and washed several times with ethanol [22]. The particles were calcined in a tube furnace at 200 °C for 3 h under high purity nitrogen environment. After that the particles ground in an agate bowl to powder form and were stored in sealed containers, marked as Mt-HAP.

Figure 1. Schematic representation for the preparation of samples.
AMX loading
20 ml AMX aqueous solution (0.5 mg ml⁻¹–3 mg⁻¹ ml⁻¹) was added into 100 ml beaker, then 1 g synthesized nanoparticles for drug carried were separated into the beaker. The mixture was stirred vigorously at room temperature for 8 h, and then centrifuged at 5000 r min⁻¹. The filtrate was collected to test the AMX concentration. At the same time, a control experiment without AMX was conducted, and the filtrate was used as a reference solution under the above conditions. The Mt-HAP loaded with AMX was processed at 50 °C under vacuum and maintained in sample bottle, and was labeled as Mt-HAP@AMX. The loaded dosage of AMX was inspected by a UV-visible spectroscopy (SPECORD 200, Analytik Jera AG) at λmax = 273 nm using the reference solution as blank control [23]. The formula for calculating the total drug load (mg g⁻¹) is as follows [24]:

\[
M (\text{mg g}^{-1}) = \frac{(C_i - C_e) \times V_{\text{AMX}}}{W_{\text{Sample}}} \times 10^3
\]

Where \(M (\text{mg g}^{-1})\) stands for drug loading efficiency, \(C_i (\text{mg ml}^{-1})\) is the initial concentration of AMX, \(C_e (\text{mg ml}^{-1})\) is the AMX concentration in medium at drug adsorption equilibrium, \(V_{\text{AMX}}(\text{ml})\) is the amount of AMX added, and \(W_{\text{Sample}}(\text{mg})\) is the mass of the drug loaded particles.

**In vitro release of drug loaded particles**

In vitro release studies of loaded particles were implemented in simulated gastrointestinal fluid (pHs 1.2 and 6.8) by dialysis technique with dissolution test apparatus (USP 6) [25]. The release temperature was set at 37 °C with the rotational frequency controlled at 150 rpm [26]. 5 ml of the mixture was removed from the solvent system and then substituted with simulation liquid of the same volume at pre-determined time intervals [27]. The drug was set free into the simulation liquid medium, and the value was monitored by UV-visible spectrometer at 273 nm based on the established UV standard absorbance curve for AMX [28].

Characterization techniques

FT-IR (SPECTRUM ONE, Perkin-Elmer, American) characterization was performed in the band of 4000–400 cm⁻¹ using KBr disks. The crystalline morphology of the samples was investigated by the XRD (D8-ADVANCE, Bruker, Germany) with Cu anode, running at 40 kV and 40 mA and scanning from 5°–60° at 4° min⁻¹. The surface topography of samples was observed by SEM (US8000, Hitachi, Japan) after coating the samples with gold film using an acceleration voltage of 6 kV. The particle size and dispersion of the powder sample were tested using a laser granulator (Mastersizer 2000, Malvern instruments, UK), with 0.1 g sample added to 1000 ml of water and tested after 30 min by ultrasonic dispersion. Thermal performance of samples was tested in a TGA instrument (PYRIS 1, Perkin-Elmer, American). The samples were roasted from 50 °C to 800 °C in alumina crucible. The heating rate was 10 °C min⁻¹ in dinitrogen atmosphere with a flow rate of 30 ml min⁻¹. N2 adsorption-desorption isotherms for samples were determined by accelerated surface area and porosimetry system (ASAP 2020 plus HD88, Micromeritics, American) after vacuum degassing. The specific surface area and pore diameter for samples were calculated through the Brunner-Emmet-Teller (BET) measurements method and adsorption branches based on the Barret-Joyner-Halenda (BJH) theory, respectively [29].

Results and discussion

**FT-IR characterization**

Infrared spectrum of Mt, Mt-CaCO₃ and Mt-HAP were recorded at the 4000–400 cm⁻¹ bands in figure 2. The positions at 3637 cm⁻¹, 1624 cm⁻¹ are seen in case of three samples, which was correspond to the –OH stretching band and –OH bending band for absorbed interlayer water in Mt, respectively [30]. The characteristic peaks were found at 1035 cm⁻¹, 520 cm⁻¹ and 467 cm⁻¹, which were related to Si–O stretching and deformation vibration. Reduction of the band intensities at 914 cm⁻¹, 843 cm⁻¹ and 793 cm⁻¹ were attributed to Al–OH/Fe–OH/Mg–OH/bending mode [31, 32]. Besides, the peaks at 1457 cm⁻¹ was recorded for antisymmetric stretching vibration of carbonate ion (figure 2(b)). The absorption peaks at 3461 cm⁻¹ and 1666 cm⁻¹ can be considered as H–O stretching and bending vibration in HAP respectively. P–O bending vibration absorption peak was also detected at 563 cm⁻¹ (figure 2(c)). The specific band of the characteristic peak of the samples are detected by infrared as shown in table 1. These infrared detection results strongly showed that CaCO₃ can be formed after Ca²⁺ ion exchange between montmorillonite layers, and finally turned into HAP.
XRD tests
The XRD curves of the samples were displayed in figure 3. Based on the Bragg’s formula [33], the layer spacing of Mt, Mt-CaCO₃ and Mt-HAP were determined as 1.23 nm, 1.37 nm and 1.43 nm, respectively. With the addition

| Samples & Wavenumber | Mt       | Mt-CaCO₃ | Mt-HAP |
|----------------------|----------|----------|--------|
| O–H stretching (H₂O)| 3633     | 3630     | 3625   |
| O–H stretching (HAP)| 3432     |          |        |
| O–H bending (HAP)   | 1666     |          |        |
| O–H bending (H₂O)   | 1628     | 1628     | 1624   |
| CO₃²⁻ Stretching CaCO₃| 1461    |          |        |
| Si–O stretching (Mt)| 1035     | 1039     | 1035   |
| Al-Mg-OH Bending (Mt)| 793; 914| 793; 914 | 793; 914|
| P–O Bending (HAP)   | 563; 609 |          |        |
| Si–O Deformation (Mt)| 467; 522| 467; 522 | 467; 522|

Figure 2. FT-IR spectra of (a) Mt, (b) Mt-CaCO₃ and (c) Mt-HAP.

Table 1. FTIR data for Mt, Mt-CaCO₃ and Mt-HAP.

Figure 3. Power XRD patterns of (a) Mt, (b) Mt-CaCO₃ and (c) Mt-HAP.
of CaCl₂ solution, the exchangeable cations between Mt layers are replaced by Ca²⁺ ions. The formation of nano calcium carbonate between Mt layers leading to an expansion in the interlayer distance. The unique diffraction peak (001) started around 6.9° (figure 3(b)), which showed that the intensity decreased and the width increased in comparison with that of original Mt (figure 3(a)) [34]. Moreover, because of the nano calcium carbonate was transformed into nano hydroxyapatite in the layers of Mt (figure 3(c)), the shift of (001) peak of Mt-HAP from 6.9° to 6.7° was accurately detected, and the d value of Mt layers increased from 1.37 nm to 1.43 nm. Separate diffraction peaks corresponding to HAP were not observed in Mt-CaCO₃ (figure 3(b)) thus supporting the conclusion that calcium carbonate transform into hydroxyapatite, which indicated that HAP were successfully pillared into the interlayer space of Mt.

**SEM observation**

The SEM photographs of Mt, Mt-CaCO₃ and Mt-HAP were presented in figure 4. The photograph (figure 4(a)) demonstrated that Mt was composed of thin sections and many small cracks formed by irregular sheet stacking. Formation of calcium carbonate particles between Mt layers can be clearly confirmed by SEM, as shown in figure 4(b). A lot of accumulated particles adhere to Mt sheets and some slits were distinctly found, which showed that the formation of calcium carbonate lead to the expansion of Mt [35]. The SEM photographs of Mt-HAP manifested similar morphologies, and the slits got smoothened after the transformation of calcium carbonate into hydroxyapatite (figure 4(c)). It was obvious that hydroxyapatite was well pillared between the layers of Montmorillonite, which was consistent with other analysis results.

**TGA analysis**

The thermal degradation of Mt, Mt-CaCO₃ and Mt-HAP upon heating under nitrogen atmosphere were investigated using TGA (figure 5). As seen, all samples show initial mass loss at 50 °C to 100 °C, which related to loss of moisture and absorbed water molecules due to strong hydrophilic characteristics of Mt.

The major weight loss was detected in the range of 500 °C–760 °C, which is mainly due to the structural decomposition of Mt. Compared to Mt (660 °C, figure 5(a)), the decomposition peak temperature of Mt-CaCO₃ (figure 5(b)) and Mt-HAP (figure 5(c)) were increased to 678 °C and 682 °C, respectively [36]. From the DTG
curves, it was clear that the formation of calcium carbonate and hydroxyapatite between montmorillonite layers supports the montmorillonite lamellae and contributes to the thermal stability of montmorillonite structure. It can be seen from the TGA curve that when the temperature is increased to 850 °C, the residual quality of the three samples is different. The results show that HAP is formed in the montmorillonite by the experimental method.

BET method
The figure 6 displayed experimental results of N2-adsorption-desorption for the original Mt, Mt-CaCO3 and Mt-HAP. Three samples have similar adsorption desorption isotherm curves. According to the International Union of Pure and Applied Chemistry (IUPAC) classification, the experimental samples were consistent with the type IV isotherm [37]. In addition, according to the shape of hysteresis loop, the adsorption-desorption curves of the three samples belong to H3 type which is given by flaky granular material, such as clay, or by fracture pore material [38]. From the figure 6, the initial stage of curve rises sharply under extremely low relative pressure (P/P0 < 0.01) due to the presence of numerous micropores and the strong adsorption of N2. Subsequently, the cured to form a platform (0.01 < P/P0 < 0.3). In the phase of relative medium pressure (0.03 < P/P0 < 0.8), compared with Mt (P = 0.40, figure 6(a)) and Mt-CaCO3 (P = 0.38, figure 6(b)), Mt-HAP began to form hysteresis loop at lower relative pressure (P = 0.33, figure 6(c)). This indicated that HAP particles help to construct more mesoporous channels between the Mt layers. Moreover, at relatively high pressures (P/P0 > 0.8), all three samples exhibited the characteristic of microporous, which were attributed to the disordered accumulation of particles resulting in slits.

As explained by the BET data in figure 6, the specific surface area and pore volume of Mt-HAP was increased dramatically from 13.6 m² g⁻¹ to 54.3 m² g⁻¹, 0.09 cm³ g⁻¹ to 0.22 cm³ g⁻¹, respectively. The increase of these values is mainly due to the formation of nano hydroxyapatite between montmorillonite layers, which increases the total specific surface area. However, compared with Mt, the pore size of Mt-HAP decreased from 3.04 nm to...
2.47 nm, which should be owed to the presence of hydroxyapatite that makes the montmorillonite channel smaller.

Effect of AMX concentration on loading capacity

The initial concentration of the AMX was changed to investigate the effect of drug concentration on the loading capacity (figure 7). With the increase of drug concentration, the drug loading was enhanced. The loading capacity basically reached a balance value, when the concentration of AMX used was increased to 2.5 mg ml$^{-1}$. Even if the drug concentration continues to increase, the drug loading will not change significantly [39]. The loading capacity of Mt, Mt-CaCO$_3$ and Mt-HAP for drugs reached 18.5 mg g$^{-1}$, 28.2 mg g$^{-1}$ and 49.1 mg g$^{-1}$ respectively. Compared with that of the other two samples, Mt-HAP has higher specific surface area and pore volume, which rendered more chances for AMX molecules embedding into the Mt layers.

Drug release characteristics in vitro

Drug release behaviors of Mt@AMX, Mt-CaCO$_3$@AMX and Mt-HAP@AMX in the simulated gastrointestinal fluids (pHs 1.2 and 6.8) were explained (figure 8). All the three samples had the ability of drug release, but showed different drug release behavior in gastrointestinal fluids. Mt@AMX exhibited more release rate than that of Mt-CaCO$_3$@AMX and Mt-HAP@AMX within 2 h in simulated gastric fluid (pH 1.2, figure 8(a)). This is due to the drug release channel between the Mt layers is not blocked, the initial release rate of the drug is very fast, and the release balance is also reached quickly. The presence of HAP and CaCO$_3$ in Mt, which makes the interlaminar channels in Mt occupied and the drug diffusion rate is slow relatively.

But after that, the drug release rate of Mt-HAP@AMX and Mt-CaCO$_3$@AMX increased significantly, reaching 65% and 58% respectively at 12 h, while the drug release rate of Mt was only 50%. This may be due to the presence of HAP and CaCO$_3$ in Mt, which makes the interlaminar channels in Mt occupied and the drug diffusion rate is slow relatively. After 2 h, HAP and CaCO$_3$ were dissolved by acid in the solution, the diffusion channels were gradually cleaned up, and the drug release rate was accelerated.

Similar drug release patterns did not appear in the simulated intestinal fluid (pH 6.8, figure 8(b)). Compared to Mt@AMX and Mt-CaCO$_3$@AMX, the drug release rate of Mt-HAP@AMX remained at a lower level. Within 12 h, the cumulative drug release rate was 49%, 41% and 30%, respectively. It was noteworthy that the release of AMX from Mt-CaCO$_3$@AMX and Mt-HAP@AMX was obviously influenced by pH of the medium. The dissolution rate of CaCO$_3$ and HAP in Mt is relatively slow in the weak acid intestinal fluid environment, which hinders the drug diffusion channel of Mt. Comparing the results of two experiments in figures 8(a), (b) can be seen that in acidic medium, the release rate of AMX is significantly faster than that of neutral medium. This can be explained as that AMX is an alkaline drug that in acidic medium helps the drug dissolve and release. In addition, acidic environments allow HAP and CaCO$_3$ to dissolve faster and drug release rates increase. The release scheme of AMX in simulated gastrointestinal fluids (pHs 1.2 and 6.8) was illustrated (figure 9). It can be concluded that the Mt-CaCO$_3$@AMX and Mt-HAP@AMX inclined to slowly release in the physiological environment of intestinal tract.
Conclusion

In this work, we have successfully prepared Mt-HAP composites which can be used for drug loading and pH response sustained release. The structure and properties of samples were investigated by FTIR, XRD, TGA, SEM and BET techniques, and the simulated in vitro release experiment were evaluated. The special surface area
and the pore volume of Mt-HAP was apparently increased from 13.6 m$^3$ g$^{-1}$ to 54.3 m$^3$ g$^{-1}$, 0.09 cm$^3$ g$^{-1}$ to 0.22 cm$^3$ g$^{-1}$, respectively. The drug loading was enhanced from 18.5 mg g$^{-1}$ to 49.1 mg g$^{-1}$. According to the results of simulated release in vitro, the original Mt had the function of drug release. The intercalation of HAP can make it have better sustained-release performance in the simulated gastrointestinal fluid, especially in the intestinal fluid with higher pH value. The cumulative release rate of AMX from Mt-HAP@AMX was 50% in pH 1.2, while it was 30% in pH 6.8 in 12 h. Therefore, environmental pH had great influence on the drug release behavior. The results of experiment indicated that the Mt-HAP has high drug loading capacity and pH-responsive sustained release ability. Finally, we can conclude that Mt-HAP drug vectors can be used for oral drug loading, especially if the drug needs to be absorbed slowly in the intestines. In this study, the drug carrier of pH response release may be used as a candidate for load anticancer drugs, although further studies need to be performed to obtain in vivo results.

Acknowledgments

This work was supported by grants from the NSFC (No. 21802041 & No.51903084), Natural Science Founding for Jiangxi Province (No. 20181BAB213006 & 20202ACBL214001), Science and Technology Project for Jiangxi Provinicial Department of transportation (No. 2016D0035).

ORCID iDs

Shaohui Wang @ https://orcid.org/0000-0001-9807-1189

References

[1] Faitelson Y, Boaz M and Dalal I 2018 Asthma, family history of drug allergy, and age predict amoxicillin allergy in children J. Aller. Cl. Imm.-Pract. 6 1363–7
[2] Singla M, Kumar H and Jindal R 2014 Solvation behavior of biologically active compounds in aqueous solutions of antibiotic drug amoxicillin at different temperatures J. Chem. Thermodynamics. 76 100–15
[3] Bruynonckx B, Stuart B, Little P, Hens N, Leven M, Butler C C, Verheij T, Goossens H and Coenen S 2018 Amoxicillin for acute lower respiratory tract infection in primary care: subgroup analysis by bacterial and viral aetiology Clin. Microbiol. Infec. 24 871–6
[4] Jafari K, Heidari M and Rahmanian O 2018 Wastewater treatment for Amoxicillin removal using magnetic adsorbent synthesized by ultrasonic process Ultrasonics-Sonchemistry 45 248–56
[5] Aycan D and Alemdar N 2018 Development of pH-responsive chitosan-based hydrogel modified with bone ash for controlled release of amoxicillin Carbohydr. Polym. 184 401–7
[6] Maral R, Majid S, Farhood N, Seyed S A and Pouneh S P 2020 Application of a novel pH-responsive gemini surfactant for delivery of curcumin molecules Mater. Res. Express 7 065403
[7] Farina M, Brundu A, Bonferoni M C, Juliano C, Rassu G, Gavini E and Cerri G 2019 Antibacterial activity of Na clinoptilolite against Helicobacter pylori: in vitro tests, synergistic effect with amoxicillin and stability of the antibiotic formulated with the zeolite Microporous Mesoporous Mater. 288 109592
[8] Rebiski E P, Souza G P, Santana S A A and Pergher S B C 2019 Bionanocomposites based on cationic and anionic layered clays as controlled release devices of amoxicillin Appl. Clay Sci. 173 35–45
[9] Dinesh R K, Anurag S, Avinash H A and Kalpana S K 2015 Molecular interactions in biomineralized hydroxyapatite amino acid modified nanoclay: in silico design of bone biomaterials Mater. Sci. Eng. C 66 207–17
[10] Saha B, Yadav S K and Sengupta S H 2018 Synthesis of nano-Hap prepared through green route and its application in oxidative desulfurization Fuel. 222 743–52
[11] Abdel Hamid D M, Abdel El-Ghani S F and Khashaba M 2018 Characterization of nano-hydroxyapatite silica gel and evaluation of its combined effect with solcoseryl paste on bone formation: an experimental study in New Zealand rabbits Future Dental J. 4 279–87
[12] Behnamasani A and Meshkini A 2019 Synthesis and engineering of mesoporous Zno@HAP heterostructure as a pH-sensitive nano-photosensitizer for chemo-photodynamic therapy of malignant tumor cells J. Drug Deliv. Sci. Tec. 53 101200
[13] Prema D, Ganavel S, Anuraj S and Gopalakrishnan C 2018 Synthesis and characterization of different chemical combination of hydroxyapatite for biomedical application Materials Today: Proceedings 5 8868–74
[14] Ma B J et al 2018 Hydroxyapatite nanobelt polyactic acid Janus membrane with osteoinduction/barrier dual functions for precise bone defect repair Acta Biomater. 71 108–17
[15] Payne S A, Katti D R and Katti K S 2016 Probing electronic structure of biominalerized hydroxyapatite inside nanoclay galleries Micron 90 78–86
[16] Chen H, Ye Z, Sun L, Li X, Shi S, Hu J, Jin Y Y, Xu Q W and Wang B L 2018 Synthesis of chitosan–based micelles for pH responsive drug release and antibacterial application Carbohydr. Polym. 189 65–71
[17] Shokrollahi F, Khodabakhshi K, Shokrollahi P, Badiani R and Moghadam Z M 2019 Atorvastatin loaded PLGA microspheres: preparation, HAp coating, drug release and effect on osteogenic differentiation of ADMSCs Int. J. Pharmaceut. 565 95–107
[18] Dening T J, Joyce P, Rao S, Thomas N and Prestidge CA 2016 Nanostructured montmorillonite clay for controlling the lipase-mediated digestion of medium chain triglycerides ACS Appl. Mater. Interfaces 8 32732–42
[19] He F R, Zhou Q F, Wang L Z, Yu G B and Feng Y H 2019 Fabrication of a sustained release delivery system for pesticides using interpenetrating polyacrylamide/alginate/montmorillonite nanocomposite hydrogels Appl. Clay Sci. 183 105347
[20] Feng D S, Shi J, Wang X J, Zhang L and Cao S K 2013 Hollow hybrid hydroxyapatite microparticles with sustained and phosphor-sensitive drug delivery properties RSCAdv. 3 24973–82
[21] Liu J Y, Chen R, Li Y R, Chen J J, Chen L H, Gao J and Li G H 2018 Microstructure-related Pb⁴⁺ adsorption capability of Ti-pillared montmorillonite in aqueous solution Clays Clay Miner. 66 666–73
[22] Reza A, Ali R M, Alexandria M Z S, Cameron L and Carpenter W 2018 Morphology and size-controlled synthesis of a metal-organic framework under ultrasound irradiation: an efficient carrier for pH responsive release of anti-cancer drugs and their applicability for adsorption of amoxicillin from aqueous solution Ultrasonics-Sonochemistry 42 594–608
[23] Franck S, Fuhrmann-Selter T, Joseph J F, Michelet R, Casilag F, Sirard J C, Wicha S and Kloft C 2019 A rapid, simple and sensitive liquid chromatography tandem mass spectrometry assay to determine amoxicillin concentrations in biological matrix of little volume Talanta 201 235–58
[24] Maximino M D, Constantino C J L, Oliveira-Jr O N and Alessio P 2019 Synergy in the interaction of amoxicillin and methylene blue with dipalmitoyl phosphatidyl choline (DPPC) monolayers Appl. Surf. Sci. 476 493–500
[25] Gleeson J P and McCartney F 2019 Striving towards the perfect in vitro oral drug absorption model Trends Pharmacol. Sci. 40 720–4
[26] Rivera A, Valdés L, Jiménez J, Pérez I, Lam A, Alstuhler E, de Ménorval L C, Fossum J O, Hansen E L and Rozynec Z 2016 Smeectite as ciprofloxacin delivery system: intercalation and temperature-controlled release properties Appl. Clay Sci. 124 140–6
[27] Li Q, Zhang W R, Wang S Y, Zhang X, Zhao Y B, Cao L Q and Sun L 2017 Construction of multifunctional porous silica nanocarriers for pH/ enzyme-responsive drug release Mater. Sci. Eng. C 81 485–91
[28] Ding C Q, Wu H W, Yin Z Z, Gao J, Wu D T, Qin Y and Kong Y 2020 Disulfide-cleavage and pH-triggered drug delivery based on a vesicle structured amphiphilic self-assembly Mater. Sci. & Eng. C 107 110366
[29] Wang J, Huang N, Peng Q, Cheng X Y and Li W K 2020 Temperature/pH dual-responsive and luminescent drug carrier based on PNIPAM-MMA/lanthanide-poloxometalates for controlled drug delivery and imaging in Hela cells Mater. Chem. and Phys. 239 121994
[30] Meenu S, Harsh K and Rajeev J 2014 Solvation behavior of biologically active compounds in aqueous solutions of antibacterial drug amoxicillin at different temperatures J. Chem. Thermodynamics. 76 100–15
[31] Li T T, Zhao L L, Zheng Z L, Zhang M, Sun Y D, Tian Q P and Zhang S Q 2018 Design and preparation acid-activated montmorillonite sustained-release drug delivery system for diclofenac in vitro and in vivo evaluations Appl. Clay Sci. 163 176–85
[32] Su M, Han F Y, Wu Y L, Yan Z P, Lv Z S, Tian D, Wang S M, Hu S J, Shen Z T and Li Z 2019 Effects of phosphate-solubilizing bacteria on phosphorous release and sorption on montmorillonite Appl. Clay Sci. 181 105227
[33] Aguzzi C, Cerezo P, Viseras C and Caramella C 2007 Use of clays as drug delivery systems: possibilities and limitations Appl. Clay Sci. 36 22–36
[34] Li T T, Zhang J, Xie X, Yin X and An X 2015 Montmorillonite-supported Ni nanoparticles for efficient hydrogen production from ethanol steam reforming Fuel. 143 55–62
[35] Zhao Y W et al 2019 Dual controlled release effect of montmorillonite loaded polymer nanoparticles for ophthalmic drug delivery Appl. Clay Sci. 180 105167
[36] Madusanka N, Sandaruwan C, Kottergoda N, Sirisena D, Munaweera I, Alwis A D, Karunaratne V and Amaratunga G A J 2017 Urea–hydroxyapatite–montmorillonite nanohybrid composites as slow release nitrogen compositions Appl. Clay Sci. 150 303–8
[37] Weng X L, Cai W L, Lin S and Chen Z L 2017 Degradation mechanism of amoxicillin using clay supported nanoscale zero-valent iron Appl. Clay Sci. 147 137–42
[38] Yu K, Zhu T H, Wu Y, Zhou X X, Yang X X, Wang J, Fang J, El-Hamshary H, Al-Deyab S S and Mo X M 2017 Incorporation of amoxicillin-loaded organic montmorillonite into poly(ester-urethane) urea nanofibers as a functional tissue engineering scaffold Colloids Surf. B Biointerf. 151 314–23
[39] Abouelmagd S A, Ellah N H A, Amen O, Abdelmozen A and Mohamed N G 2019 Self-assembled tannic acid complexes for pH-responsive delivery of antibiotics: role of drug-carrier interactions Int. J. Pharm. 562 76–85