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**Effects of Polymer Intercalation in Calcium Silicate Hydrates on
Drug Loading Capacities and Drug Release Kinetics: An X-ray
Absorption Near Edge Structure Study**

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Draft

Abstract

Different calcium silicate hydrate (CSH)/polymer composites are synthesized by using a controlled precipitation reaction between calcium salt and silicate salt, followed by the addition of various polymer solutions at room temperature. X-ray absorption near edge structure (XANES) spectroscopy has been used to extensively investigate the structural changes after hybrid biomaterials formation and the drug-carrier interactions on the molecular level. We find that the polymers alter the structure of CSH to various degrees, and that this behaviour further influences the drug loading capacities (DLCs) and drug release kinetics.

Keywords

Calcium silicate hydrate, Drug loading, Drug release, Polymer intercalation, X-ray absorption spectroscopy

Introduction

Currently, composite biomaterials comprising inorganic biomaterials (bioceramics) and organic polymers are more attractive, since their combination improves their mechanical properties and stabilities, further enhances tissue interactions.¹ With increasing demands for biomaterials to deliver drugs to local hard-tissue sites in order to increase the effectiveness of the therapy, efforts have been invested in developing composite biomaterials with a drug-delivery capacity.²⁻⁵ However, little has been known about the effects of the introductions of organic materials on drug loading capacities and drug release kinetics, which are largely influenced by the structure of drug carriers including pore size, pore volume and surface areas, *etc.*, and interactions between drug carriers and drug molecules.⁶⁻⁸

X-ray absorption near edge structure (XANES), the near edge region of the X-ray absorption spectroscopy (XAS) has gained popularity in the structural analysis in the last two decades because it provides information about the immediate surroundings of the absorbing atom and it is sensitive to the oxidation state and local symmetry of elements of interest.⁹ Hence, XANES is a perfect technique to study the structural changes of biomaterials composites before and after polymer incorporation, and to track the interactions between drug molecules and bioceramics/polymer composites at different elements/edges.

So far, calcium silicate hydrate (CSH) has gained more and more favours on hard tissue regeneration and augmentation because of its impressive stimulatory effect on osteogenic differentiation of stem cells.¹⁰⁻¹² With the help of scanning transmission X-ray microscopy, Ha *et al.*¹³ have investigated the carbonation of calcium silicate hydrate (CSH) after the formation of CSH/polyethylene glycol (PEG) and CSH/hexadecyltrimethylammonium bromide (HDTMA) composites. However, the use of XANES to study CSH/polymers composites as drug carriers in

drug delivery systems has yet to be reported. Herein, we report a controlled precipitation synthesis of CSH nanosheets, followed by a room-temperature solution preparation of three CSH/block copolymer composites by the incorporation of one each of the three different block copolymers: polyvinyl alcohol (PVA); monomethoxy (polyethyleneglycol)-block-poly(DL-lactide-co-glycolide) (mPEG-PLGA) and poly(diallyldimethylammonium chloride) (PDDA). Ibuprofen (IBU), a typical anti-inflammatory drug is further employed for the investigations of drug loading and release properties of these polymer incorporated composites (Scheme 1). XANES is utilized to study the structural changes of CSH after the formation of CSH/polymer composite and the interactions between IBU and CSH/polymer composite in order to provide insights for drug loading capacities enhancement and controllable drug release profiles.

Experimental

Materials

$\text{Na}_2\text{SiO}_3 \cdot 9\text{H}_2\text{O}$, $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$, $\text{NH}_3 \cdot \text{H}_2\text{O}$, polyvinyl alcohol (PVA, $M_w = 1750 \pm 50$) were purchased from Sinopharm Chemical Reagent Co., Ltd. Monomethoxy (polyethyleneglycol)-block-poly(DL-lactide-co-glycolide) (mPEG-PLGA) (mPEG-PLGA, $M_w = 8000$; the molecular weight of the mPEG segment was 5000 and the molar ratio of DL-lactide to glycolide was 75:25.) was purchased from Jinan Daigang Biomaterial Co., Ltd. Poly(diallyldimethylammonium chloride) (PDDA, M_w 100,000-200,000, 20 wt. % in H_2O) was purchased from Sigma-Aldrich. Ibuprofen (IBU) was purchased from Shanghai Yuanji Chemical Co., Ltd. The phosphate buffer saline (PBS, pH = 7.4 at 37 °C) was purchased from Bio Basic Inc. All the purchased chemicals were used as received without further purification.

Preparation of CSH/polymer Composites

Calcium silicate hydrate nanosheets were prepared by a reaction rate-controlled solution precipitation method.¹⁴ For the preparation of CSH/polymer composites, solution A was prepared by dissolving 0.853 g of $\text{Na}_2\text{SiO}_3 \cdot 9\text{H}_2\text{O}$ into 50 mL deionized water, into which 5 mL of 0.6 M $\text{Ca}(\text{NO}_3)_2$ aqueous solution was injected at a constant rate of $2.5 \text{ mL} \cdot \text{h}^{-1}$ under magnetic stirring for 3 hours; followed by addition of 1 mL of aqueous ammonia (~27%). Solution B was 10 mL of 10% PDDA aqueous solution; Solution C and D were prepared by dissolving 0.5 g of mPEG-PLGA into 10 mL deionized water and 1 g of PVA into 10 mL deionized water, respectively. Then 25 mL of solution A was added into solution B, C, D, respectively, and stirred at room temperature for 8 days. The CSH/polymer composites were collected by centrifugation, washed with deionized water three times and absolute ethanol once, and then dried at 60 °C.

IBU drug loading and *in vitro* drug release

0.02 g of CSH/PDDA, 0.1 g of CSH/mPEG-PLGA and 0.035 g of CSH/PVA as synthesized composites were added into 1 mL, 5 mL, and 1.75 mL IBU hexane solution ($40 \text{ mg} \cdot \text{mL}^{-1}$) in different flasks at room temperature, respectively. The flask was immediately sealed to prevent hexane from evaporation, and the mixture was treated by ultrasound for 2 minutes. Then the flask was oscillated at a constant rate of 160 rpm at 37 °C for 24 hours. After that the product was separated by centrifugation, washed with hexane once, and dried in air at 60 °C. Then the as-prepared IBU-loaded CSH/polymer composites each (20 mg) were immersed in a 40 mL phosphate buffered saline (PBS) at 37 °C under shaking at a constant rate. The IBU release medium (2.0 mL) was extracted for UV-Vis analysis at the wavelength of 263 nm at given time intervals.

Characterization

The morphologies of CSH/polymer composites before and after IBU loading were obtained with a transmission electron microscope (TEM, Philips CM-10) at Biotron Lab, University of Western Ontario. The thermogravimetric (TG) curves were measured on a STA 409/PC simultaneous thermal analyzer (Netzsch, Germany) with a heating rate of $10\text{ }^{\circ}\text{C min}^{-1}$ in blowing air to measure the drug loading capacities of CSH/polymer composites, and the drug loading capacity of CSH nanosheets was also measured for comparison. Fourier transform infrared (FTIR) spectra were recorded on a FTIR spectrometer (FTIR-7600, Lambda, Australia). The compositions of CSH/polymer composites were characterized by X-ray powder diffraction (XRD, Rigaku D/max 2550 V, Cu $K\alpha$ radiation, $\lambda = 1.54178\text{ }\text{\AA}$).

XANES Measurement

XANES measurements were conducted at the Canadian Light Source (CLS) using the Soft X-ray Microcharacterization Beamline (SXRMB), which is equipped with a double crystal monochromator with two sets of interchangeable crystals operating with an energy range of 1.7 to 10 keV. The InSb (111) crystals were used for the Si K-edge XANES measurements while the Si (111) crystals were used for the Ca K-edge XANES. The detection modes were total electron yield (TEY) and X-ray fluorescence yield (FLY) recorded with a Si drift solid state detector, tracking with surface and bulk sensitivities, respectively.

FEFF Calculation

FEFF is a computer code based on real space multiple scattering theory which allows for the mathematical modeling of XANES and EXAFS. The crystal structure of the as-synthesized CSH nanosheets was reported to be consistent with the distorted 1.4 nm tobermorite $(\text{Ca}_5\text{Si}_6\text{O}_{16}(\text{OH})_2 \cdot 8\text{H}_2\text{O})$,¹⁴ and has a space group symmetry of B_{11b} with a lattice constant of $a = 6.735\text{ }\text{\AA}$, $b = 7.425\text{ }\text{\AA}$, $c = 27.987\text{ }\text{\AA}$, $\gamma = 123.25^{\circ}$. The locations of the atoms in $\text{Ca}_5\text{Si}_6\text{O}_{16}(\text{OH})_2$

are Ca₁ at (0.737, 0.425, 0.2852), Ca₂ at (0.879, 0.994, 0.0019) Ca₃ at (0.251, 0.428, 0.2147), Si₁ at (0.750, 0.386, 0.1752), Si₂ at (0.895, 0.750, 0.1041), Si₃ at (0.743, 0.961, 0.1751), O₁ at (0.752, 0.512, 0.1248), O₂ at (0.760, 0.189, 0.1542), O₃ at (0.972, 0.554, 0.2070), O₄ at (0.518, 0.301, 0.2065), O₅ at (0.887, 0.250, -0.0482), OH₆ at (0.182, 0.888, 0.1175), O₇ at (0.759, 0.860, 0.1252), O₈ at (0.501, 0.824, 0.2067), O₉ at (0.982, 0.033, 0.2069).¹⁵ To set up a calculation, the above positions of the atomic clusters are input into the FEFF software. The positions can be generated by the crystal parameters, including the space group, unit cell parameters, and the atomic coordination in the unit cell *etc.*

Results and Discussion

Effects of Polymer Introduction on the Structural Changes of CSH Nanosheets

The morphologies of CSH nanosheets, various CSH/polymer composites before and after IBU loading have been characterized by transmission electron spectroscopy, as shown in Figure 1. One can see that the specimens consist of wrapped nanosheets and these nanosheets stack together (Figure 1(a)). However different polymer incorporations and IBU loadings (Figure 1(b) to (h)) do not alter the morphology of CSH nanosheets significantly. The FTIR spectra of the CSH nanosheets and CSH/polymer composites are shown in Figure 2(a). For CSH nanosheets, the absorption bands in the range of 900-1100 cm⁻¹ and 3000-3700 cm⁻¹ are the stretching vibration of Si-O bonds and O-H groups in water, respectively; and the absorption at around 1630 cm⁻¹ is assigned to the bending vibration of the adsorbed water. After addition of different polymers, there are no significant FTIR changes except the more noticeable absorptions at around 2800-2900 cm⁻¹, which are due to C-H stretching from polymer molecules.^{16,17}

XRD patterns of CSH nanosheets and their polymer composites were obtained, as shown in Figure 2(b). The crystal phase of CSH nanosheets is consistent with that of the 1.4 nm tobermorite-like structure ($\text{Ca}_5\text{Si}_6\text{O}_{16}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ JCPDS: 29-0331). Upon composites formation, there are no significant changes for CSH/PDDA composite (red); however, for CSH/mPEG-PLGA (navy) and CSH/PVA (dark cyan) composites, there are new patterns at around 18-19°. Matsuyama *et al.*¹⁸ reported that these new patterns can be ascribed to the precipitated polymers themselves.

XANES tracks if there is any local structural changes of the CSH nanosheets after different the formation of CSH/polymers composites. Figure 3(a) and (b) show the Ca K-edge XANES and the first derivative spectra of CSH nanosheets and their polymers composites. At the Ca K-edge XANES, we will focus on the following discussions using the TEY XANES spectra because there are no detectable spectral differences between TEY and FLY spectra, indicating that the specimens are homogeneous before and after different polymer composites formation and they are thin, hence suffer little thickness effect (comparisons of TEY and FLY spectra at the Ca K-edge can be found in the supporting information).

There are several discernible XANES features, labelled from “a” to “d”. The most intense peak (feature “c”) is due to Ca 1s to 4p dipole transition. The pre-edge peak (feature “a”) and the shoulder “b” are dipole forbidden; however they can be still observed weakly because of the hybridization of Ca with ligand states of p-character, leading to the departure from perfect Ca crystal symmetry. Although feature “d” is mainly from multiple scattering processes, it is very sensitive to the immediate surroundings of Ca.¹⁹⁻²¹

Compared with the FTIR results, the XANES spectra are more sensitive to the local structure changes after the formation of CSH/polymer composites. Although the spectra of CSH/PDDA

(red profile) and CSH/mPEG-PLGA (navy) are very similar to that of CSH nanosheets (black), after close examination of the spectrum of CSH/PVA (dark cyan), two subtle though clearly noticeable changes are observed compared with CSH nanosheets alone (black curve): one is at the edge jump region (labelled “b”, 4040 - 4045 eV), where a tiny new feature appears in the first derivative of the spectrum (Figure 3(b)), indicated by the dashed arrows; the other is feature “d” after the formation of CSH/PVA composite, which is less prominent than the other specimens, and it can be also observed in the derivative spectra between 4055 - 4060 eV. The crystal structure of CSH nanosheets with tobermorite-like structure were illustrated by FEFF 9, shown in Figure 4. (1.4 nm indicates the interlayer spacing between two consecutive Ca-O layers which are flanked by silicate chains). Tobermorite is formed by central Ca-O octahedral sheets, connected on both sides to silicate tetrahedral chains. The space between two layers contains additional calcium cations and water molecules to balance the charge.¹⁵ Matsuyama *et al.*^{18,22} reported that the more compact nature of PVA molecule (~0.45 nm) provided the possibility of intercalation within the structure of CSH. As a result, although the PVA insertion did not change the structure of CSH completely, the hydrogen bonding between PVA and Ca-OH in the interlayer can slightly increase the basal spacing of CSH.^{18,22,23} As a result, in terms of the XANES changes, the interaction between PVA and Ca-OH groups slightly modifies the hybridization of Ca with ligand states (changes of feature “b”) and the increase of interlayer space alters the multiple scattering pathways of CSH (change of feature “d”). On the other hand, the reason why we cannot observe the significant spectral differences from CSH, CSH/mPEG-PLGA and CSH/PDDA compositions is because of the failure of mPEG-PLGA and PDDA intercalation into CSH structure. This can be ascribed to the steric effects or larger chain

diameter of the polymer; and the cationic N^+ ions interact with Ca ions repulsively for PDDA polymer.

Hence mPEG-PLGA and PDDA can only adsorb on the surface of CSH nanosheets, resulting in the change of local structure of silicate tetrahedral significantly, which are reflected in Figure 3(c) and (d). At the Si K-edge, for the CSH nanosheets (black curve), there is only one peak (“a”), which is ascribed to the Si 1s to 3p transition in a Si-O tetrahedral environment.^{24,25} For all of the CSH/polymer composites spectra (red, navy, and dark cyan curves), it is interesting to note that a new feature “b” emerged at a lower energy of the main resonance in TEY spectra only (Figure 3(c)), while their FLY spectra are very similar (Figure 3(d)). This new feature is due to the adsorption of different polymers on the surface of the CSH nanosheets, inducing the distortion of silicate tetrahedron on the surface.^{26,27} Since PVA can intercalate into interlayers of CSH structure based on the Ca K-edge results, there is only a subtle change at its Si K-edge XANES, indicating PVA molecules mainly interact with Ca-OH groups in the interlayer and change the local structure of Ca when they are intercalated into the structure of CSH.

Based on the results of the Ca and Si K-edge XANES, we propose the following interactions between CSH and different polymer molecules, as shown in Figure 4. All of the PDDA, mPEG-PLGA and PVA molecules may distort silicate tetrahedra by adsorption on the surface; while only PVA can intercalate into the interlayers of CSH structure and changes the Ca local structures because of the more compact nature of PVA chains.

Interactions between CSH/polymer Composites and IBU Molecules

Figure 5(a) shows the Ca K-edge XANES spectra of CSH nanosheets and their polymer composites before and after IBU loading. Similar to the situation before IBU loading, there are no detectable differences between TEY and FLY of CSH/polymer composites with IBU loading.

231 However, compared with the spectra before IBU loading, there are several distinct changes;
232 especially prominent at the features “b” and “d” in the first derivative spectra (Figure 5(b)). In
233 the case of CSH nanosheets, CSH/mPEG-PLGA and CSH/PDDA composites, before IBU
234 loading, there are only two peaks between 4040-4050 eV in the derivative spectra of feature “b”,
235 but three peaks appear after the drug is loaded; moreover, the shoulder feature “d” smears out in
236 all the spectra after IBU loading (Figure 5a). These changes are due to the interactions between
237 Ca-OH groups and carboxylic acid groups of IBU molecules, as illustrated in a previous study;
238 the loading of IBU distorts the local order of Ca (more amorphous).²⁸ What is more interesting
239 is the observation that the spectral changes after IBU loading into CSH/PVA composites: the
240 spectrum (dark cyan) after IBU loading is different from all the other three spectra. This may be
241 due to the interactions among IBU, PVA molecules and interlayer Ca-OH groups since PVA has
242 been intercalated into the structure of CSH already (Scheme 2).

243 The effect of IBU loading on the silicate local environment has been studied via the Si K-edge
244 XANES spectra, as shown in Figure 5(c) and (d). After IBU loading, feature “b” can only
245 observed in the TEY of IBU loading samples, which can be ascribed to the combined
246 interactions between different polymers, IBU molecules and silanol groups (-Si-OH), especially
247 for the CSH/mPEG-PLGA-IBU, which has a more intense peak at around 1843 eV (Scheme 3).

248 Additionally, the IBU loading changes the main resonance “a” as well (both in TEY and FLY):
249 the main resonance becomes sharper and shifts to higher energy by 0.2 eV. This can be ascribed
250 to the preference of electrostatic interactions between Ca-OH, silanol groups and IBU: the
251 electrostatic interaction is stronger between Ca and IBU than that between silanol groups and
252 IBU (due to the activity of Ca-OH, Si-OH to carboxylic acid), making original silicate
253 environment a more “isolated” tetrahedral environment, hence the width of the main resonance at

the Si K-edge TEY and FY turns narrower and becomes more tetrahedral SiO_4 like (reference spectra of CSH and SiO_2 shown in the supporting information). The FTIR spectra of the CSH nanosheets and CSH/polymer composites before and after IBU loading are shown in Figure 6, which support the XANES analysis. The more prominent C–H stretching ($\sim 2800\text{--}3000\text{ cm}^{-1}$), and the appearance of C=O ($\sim 1560\text{ cm}^{-1}$) stretching peaks indicate that IBU has been loaded on the nanosheets and composites. Nevertheless the red shift of C=O stretching vibration (normally located around 1700 cm^{-1}) indicates the interactions between the CSH/polymer composites and the –COOH groups of IBU drug molecules.¹⁶ Besides, the blue shift of Si–O stretching vibration from 975 cm^{-1} to 1083 cm^{-1} also supports this IBU-silanol group interaction: increase the polarity of the Si–O group while reduce the polarity of the C=O group, which results in the blue and red shifts in the FTIR spectra mentioned above (silicate tetrahedral distortion accompanied by a better screened Si site).

Effects of Different Polymer Introduction on Drug Loading Capacities and Drug Release Kinetics

After demonstrating that the introduction of different polymers changes the structures of CSH by the analysis of XANES, especially that of the CSH/PVA composites, it would be necessary to investigate whether or not the PVA intercalation may influence the drug loading capacities (DLCs) and drug release kinetics. Hence, IBU loading capacities into different CSH/polymer composites are shown in Figure 7(a). Compared with the CSH nanosheets alone, all the DLCs of IBU decrease to some extent after the formation of CSH-polymer composites. This is due to the interactions between different polymers and CSH nanosheets: parts of the active sites (Ca–OH and Si–OH groups) interact with different polymers molecules, leading to the reduction of the number of active sites for the IBU molecules' attachment. It should be noted that the IBU DLC

of CSH/mPEG-PLGA decreases significantly compared with that of CSH nanosheets. One reason is due to the strong interactions between CSH and polymers mentioned above, the other is the steric and entropic effects, which is one of the key factors to prevent the IBU molecules' attachment on the surface of CSH/polymer composites.

Figure 7(b) shows the IBU drug release profiles of the IBU-CSH/polymer composites drug delivery systems in the PBS medium. In our previous study, it is shown that the CSH drug carriers alone do not exhibit the ability of good controlled drug release: there was a burst drug release effect at the early stage; about 97-98 % of loaded IBU were released in the first several hours,²⁹ and so are the situations of CSH/PDDA and CSH/mPEG-PLGA in this study. However, compared with the other two composites, the CSH/PVA-IBU system shows relatively more controlled drug release kinetics, which is largely due to the intercalation of PVA into the CSH structures, and the combined effects of PVA and IBU on the structural changes of Ca ions slowing down the IBU release from the CSH/PVA composite.

Conclusions

In this study, we have shown the structural changes of CSH nanosheets upon the formation of different polymers composites and the incorporation of IBU molecules by XANES analysis as summarized below.

- PVA molecules can intercalate into to the interlayer of CSH structures and as a result modify the local structure of interlayer Ca and silicate tetrahedra on the surface; while mPEG-PLGA and PDDA can only adsorb on the surface of CSH nanosheets leading to the distortion the silicate tetrahedral chains on the surface because of the steric effects.

- The IBU loading on these CSH/polymer composites further changes the local structure of Ca and silicate simultaneously by the interactions between the carboxylic groups of IBU and the Ca-OH and Si-OH groups of CSH, which has been extensively studied previously.
- However, the drug loading capacities of IBU is restrained from the incorporation of polymer into the CSH because the active sites for drug molecules attachment have been reduced by the interaction with different polymers.
- Compared with the other two composite systems, the CSH/PVA composite has a relatively better controlled drug release kinetic profile. We attribute this behavior to the PVA intercalation into CSH structures and has a combined effect with IBU on the structure of interlayer Ca ions after drug loading.

Finally, we have demonstrated that XANES is a sensitive tool to track these effects from different elemental point of view, and this opens up future possibilities for the study of drug delivery and drug release from drug carriers and their composites.

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References

- (1) Rezwan, K.; Chen, Q. Z.; Blaker, J. J.; Boccaccini, A. R. *Biomaterials* **2006**, 27, 3413.

- 322 (2) Dou, Y. D.; Wu, C. T.; Chang, J. *Acta Biomater.* **2012**, *8*, 4139.
- 323 (3) Wei, J.; Chen, F. P.; Shin, J. W.; Hong, H.; Dai, C. L.; Su, J. C.; Liu, C. S. *Biomaterials*
324 **2009**, *30*, 1080.
- 325 (4) Wu, J.; Zhu, Y. J.; Chen, F.; Zhao, X. Y.; Zhao, J.; Qi, C. *Dalton Trans.* **2013**, *42*, 7032.
- 326 (5) Cheng, W.; Li, H. Y.; Chang, J. *Mater. Lett.* **2005**, *59*, 2214.
- 327 (6) Ramila, A.; Munoz, B.; Perez-Pariente, J.; Vallet-Regi, M. *J. Sol-Gel Sci. Technol.* **2003**,
328 *26*, 1199.
- 329 (7) Wang, S. B. *Micropor. Mesopor. Mater.* **2009**, *117*, 1.
- 330 (8) Vallet-Regi, M.; Balas, F.; Arcos, D. *Angew. Chem. Int. Edit.* **2007**, *46*, 7548.
- 331 (9) Sham, T. K. *Int. J. Nanotechnol.* **2008**, *5*, 1194.
- 332 (10) Ding, S.-J.; Shie, M.-Y.; Wang, C.-Y. *J. Mater. Chem.* **2009**, *19*, 1183.
- 333 (11) Wu, C.-T.; Chang, J. *J. Inorgan. Mater.* **2013**, *28*, 29.
- 334 (12) Hughes, E.; Yanni, T.; Jamshidi, P.; Grover, L. M. *Adv. Appl. Ceram.* **2015**, *114*, 65.
- 335 (13) Ha, J.; Chae, S.; Chou, K. W.; Tyliczszak, T.; Monteiro, P. J. M. *J. Mater. Sci.* **2012**, *47*,
336 976.
- 337 (14) Wu, J.; Zhu, Y. J.; Chen, F. *Small* **2013**, *9*, 2911.
- 338 (15) Bonaccorsi, E.; Merlino, S.; Kampf, A. R. *J. Am. Ceram. Soc.* **2005**, *88*, 505.
- 339 (16) Stuart, B. H. *Infrared Spectroscopy: Fundamentals and Applications*; Wiley, 2004.
- 340 (17) Yu, P.; Kirkpatrick, R. J.; Poe, B.; McMillan, P. F.; Cong, X. D. *J. Am. Ceram. Soc.* **1999**,
341 *82*, 742.
- 342 (18) Matsuyama, H.; Young, J. F. *J. Mater. Res.* **1999**, *14*, 3379.
- 343 (19) Yamamoto, T. *X-Ray Spectrom.* **2008**, *37*, 572.
- 344 (20) Eichert, D.; Salome, M.; Banu, M.; Susini, J.; Rey, C. *Spectrochim. Acta B* **2005**, *60*, 850.

- 345 (21) Cormier, L.; Neuville, D. R. *Chem. Geol.* **2004**, *213*, 103.
- 346 (22) Matsuyama, H.; Young, J. F. *Chem. Mater.* **1999**, *11*, 16.
- 347 (23) Matsuyama, H.; Young, J. F. *J. Mater. Res.* **1999**, *14*, 3389.
- 348 (24) Li, D.; Bancroft, G. M.; Kasrai, M.; Fleet, M. E.; Feng, X. H.; Tan, K. H.; Yang, B. X.
- 349 *Solid State Commun.* **1993**, *87*, 613.
- 350 (25) Li, D.; Bancroft, G. M.; Fleet, M. E.; Feng, X. H. *Phys Chem Miner* **1995**, *22*, 115.
- 351 (26) Sutherland, D. G. J.; Kasrai, M.; Bancroft, G. M.; Liu, Z. F.; Tan, K. H. *Phys Rev B* **1993**,
- 352 *48*, 14989.
- 353 (27) Chaboy, J.; Barranco, A.; Yanguas-Gil, A.; Yubero, F.; Gonzalez-Elipe, A. R. *Phys. Rev.*
- 354 *B* **2007**, *75*.
- 355 (28) Guo, X.; Wu, J.; Yiu, Y.-M.; Hu, Y.; Zhu, Y.-J.; Sham, T.-K. *Phys. Chem. Chem. Phys.*
- 356 **2013**, *15*, 15033.
- 357 (29) Guo, X.; Wang, Z.; Wu, J.; Hu, Y.; Wang, J.; Zhu, Y.-J.; Sham, T.-K. *CrystEngComm*
- 358 **2015**.

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361 Scheme 1. Chemical structures of different polymers and ibuprofen.

Figure 1. TEM images of CSH nanosheets and CSH/polymer composites before and after IBU loading: (a) CSH, (b) CSH/PDDA, (c) CSH/mPEG-PLGA, (d) CSH/PVA, (e) CSH-IBU, (f) CSH/PDDA-IBU, (g) CSH/mPEG-PLGA-IBU, (h) CSH/PVA-IBU.

Figure 2. FTIR spectra (a) and XRD patterns (b) of CSH nanosheets, and different CSH/polymer composites.

Figure 3. XANES spectra of CSH/polymer composites at the Ca and Si K-edge, respectively. (a) Ca K-edge TEY spectra; (b) Ca K-edge first derivative spectra; (dashed arrows in (b) indicate the changes of CSH/PVA composite compared with CSH nanosheets) (c) Si K-edge TEY spectra; (d) Si K-edge FLY spectra.

Figure 4 Schematic illustration of crystal structure of 1.4 nm tobermorite (green, red and beige spheres stand for Ca, O and Si atoms, respectively; $\alpha=90^\circ$, $\beta=90^\circ$, and $\gamma=123.25^\circ$) and the interactions between CSH and different polymers (PVA, mPEG-PLGA and PDDA are represented by navy triangle, orange rectangle and green trapezoid, respectively).

Scheme 2. Interactions between CSH, IBU and PVA on the local structure of Ca in the interlayer of CSH.

Scheme 3. Interactions between CSH, IBU and polymers on the local structure of silicate on the surface.

Figure 5. Comparisons of XANES spectra of CSH/polymer composites before and after IBU loading (a) Ca K-edge TEY and (b) first derivative spectra; (c) Si K-edge TEY spectra; (d) Si K-edge FLY spectra.

Figure 6. Comparisons of FTIR spectra of CSH nanosheets, CSH/polymer composites before and after IBU drug loading.

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399 Figure 7. (a) IBU drug loading capacities (DLCs) of different CSH/polymer composites (the
400 DLCs of CSH nanosheets for comparison); (b) IBU Release profiles of different CSH/polymer
401 composites.