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PAPER

Luminescent Hollow $CaWO_4$ Microspheres: Template-Free Synthesis, Characterization and Application in Drug Delivery

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Luminescent porous micro/nano-structures have gained much attention in recent years due to their potential applications in biomedicine fields. Herein, we report the well-dispersed luminescent hollow structural $CaWO_4$ microspheres prepared by a facile hydrothermal method without addition of any templates and additives. The phase, morphology and pore structures of hollow $CaWO_4$ microspheres were well characterized by X-ray diffraction (XRD), scanning electron microscopy (SEM) and N_2 adsorption/desorption. It is observed that the resultant $CaWO_4$ microspheres possess a hollow structure with mesoporous shell and have good biocompatibility, making them suitable to be used as drug carriers. Subsequently, ibuprofen (IBU), a typical anti-inflammatory drug, was successfully loaded into the $CaWO_4$ microspheres and the drug release behavior was investigated. It is found that IBU molecules were successfully introduced into the inner space and mesopores of $CaWO_4$ microspheres and there exist strong interaction between IBU molecules and $CaWO_4$ microspheres. The IBU release from $CaWO_4$ microspheres exhibit a sustained-release property and two-step release mechanism. In addition, the hollow structural $CaWO_4$ microspheres also exhibit bright blue emission after loading of IBU. These results indicate that the luminescent hollow $CaWO_4$ microspheres have promising prospect in the sustained drug release systems and tracking drug release process.

1. Introduction

In recent years, inorganic luminescent materials with hollow structure have attracted much attention because of their potentially numerous applications in many fields, such as catalysis, drug delivery, sensors, and cell imaging.[1-7] In particular, hollow structural materials are considered to be ideal candidates as drug carrier because of their larger cavity and mesopores distributed in the shells.[8, 9] The large cavity can be acted as an effective storage to load more drug molecules. What is more, the mesopores can delay drug release due to the pore confinement,[10, 11] resulting in prolongation of the drug action and reduction of the dose frequency. On the other hand, inorganic luminescent materials have gained great interest because they can be employed as a probe to monitor or track the drug release process and evaluate the drug release efficiency.[12, 13] Consequently, the benefits of combined hollow structures and luminescent property will undoubtedly attract researchers' attention in terms of biomedical application. Currently, many luminescent hollow structures based on rare earth ions doped compound (e.g., rare earth oxide, fluoride and inorganic oxysalt) have been reported in recent years.[7, 14-23] However, the potential biocytotoxicity of rare earth elements possibly restrict their application in biomedical fields.[24, 25]

In contrast, metal tungstate materials have gained numerous interests owing to their self-activated luminescent properties without rare-earth ion doping. Over the past decades, several metal tungstates with hollow structure have been fabricated via template-direct approach or additional additives in the synthesis system.[26-29] For instance, Zhou et al. synthesized the hollow $BaWO_4$ nanospheres using polymer polyvinyl pyrrolidone micelle as template.[26] Zhao et al. prepared $BaWO_4$ hollow spheres by a precipitation route in the presence of poly (methacrylic acid).[27] Wang and co-workers prepared hierarchically porous β-Ag_2WO_4 hollow nanospheres using poly (methacrylic acid) (PMAA) as soft template.[28] As a member of the metal tungstate family, $CaWO_4$ is one of the most important materials. However, up to now, only a few works have reported the preparation of hollow structural $CaWO_4$ materials. Wang et al. prepared hollow $CaWO_4$ microspheres by the hydrothermal method in the presence of sodium dodecyl sulfate (SDS).[30] Jiang et al. reported rare earth ion (Tb^{3+}) doped $CaWO_4$ hollow microspheres with 3-4 μm diameter using glycine as the structure directing agent.[31] Undoubtedly, the usage of templates or other additives will introduce heterogeneous impurities and increase production costs. Moreover, some templates have to be removed by calcination or etching, which result in a complicated process and wasting of energy

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and polluting the environment. Therefore, it is highly desirable to develop a facile, and environmentally friendly method to prepare hollow structural $CaWO_4$ micro/nanostructures. However, to the best of our knowledge, the synthesis of hollow structural $CaWO_4$ microspheres has not been reported by a facial hydrothermal method without addition of any templates and additives. In addition, luminescent hollow structural $CaWO_4$ microspheres have great potential application in drug delivery systems. First, the large cavity and small pores in the shell can be used as storage for controlled release of drugs. Second, the excellent luminescence properties of $CaWO_4$ make them to track the route of the drug loaded carrier.

In this work, luminescent hollow structural $CaWO_4$ microspheres were prepared by a template-free, facile hydrothermal method. The pore structures of $CaWO_4$ microspheres were characterized by N_2 adsorption/desorption measurement. The results show that the resultant $CaWO_4$ microspheres possess a mesoporous shell and huge cavity in the surface. Ibuprofen (IBU), a typical anti-inflammatory drug, was selected as a model drug to investigate the drug loading and release properties. The interaction between IBU molecules and $CaWO_4$ carriers were studied by FT-IR and TGA. Also, the drug release behavior and mechanism of IBU from carrier was investigated in detail.

2. Experimental

2.1 Synthesis of luminescent hollow $CaWO_4$ microspheres

The luminescent hollow $CaWO_4$ microspheres were synthesized through a template-free hydrothermal process. Typically, 0.22 g of anhydrous $CaCl_2$ and 0.66 g of $Na_2WO_4{\cdot}2H_2O$ were dissolved in 10 mL of deionized water and treated with ultrasonator for 5 min to form homogenous solution A and B, respectively. Then, the aqueous solution B was poured into the solution A under stirring at 70 ^oC in an oil bath. After stirring for 5 min, the mixture was transferred into a 30 mL Teflon-lined autoclave with a stainless steel shell. The autoclave was sealed and heated to 140 °C for 20 h, then cooled to room temperature naturally. The obtained precipitates were separated by centrifugation and washed several times with deionized water and ethanol in sequence. The obtained white particles were dried in air at 80 °C for 12 h. For comparison, another type of hollow $CaWO_4$ microspheres were also synthesized using sodium dodecyl sulfate (SDS) as template according to method reported by Wang,[30] and the obtained materials were denoted as T-$CaWO_4$.

2.2 Drug loading and release

The drug IBU was loaded into the hollow $CaWO_4$ microspheres by an impregnation method. Typically, 100 mg of $CaWO_4$ microspheres were dispersed into a solution of IBU (1.0 mg/mL) in 20 mL of ethanol under stirring at room temperature for 12 h, then the mixed suspension was collected by centrifugation and washed twice with ethanol. Then, the collected precipitates were dried at 60 °C for 12 h, and donated as $CaWO_4$-IBU. A physical mixture of $CaWO_4$ and IBU was prepared by intimated mixing of $CaWO_4$ (100 mg) and IBU (4 mg) (mass ratio 25/1, IBU content 4 wt %) in an agate mortar.

The drug release test *in vitro* was performed as follows: 50 mg of IBU loaded hollow $CaWO_4$ microspheres were immersed into 10 mL of PBS solution (pH 7.4) at 37 ^oC with gentle shaking. At a given time, 2 mL of PBS was withdrawn and replaced with equal volume of the corresponding fresh PBS to maintain a constant volume. The amount of release IBU was determined by a UV-vis spectrophotometer at 272 nm.

2.3 *In vitro* cytotoxicity of hollow $CaWO_4$ microspheres

The *in vitro* cytotoxicity of hollow $CaWO_4$ microspheres were measured by MTT assay on human mesenchymal stem cells (hMSCs). Cells with a density of 7500 cells per well were cultured in a 96-well plate in 5% CO_2 and 37 °C for 24 h. Then different concentrations of hollow $CaWO_4$ microspheres (0, 0.1, 0.2, 0.4 and 0.8 mg/mL) were added to the culture wells and subsequently incubated for 24 h at 37 °C in 5% CO_2. At the end of incubation time, 20 μL of 5 mg/μL MTT (3-(4, 5-dimethyl-2-thiazolyl)-2, 5-diphenyl-2-H-tetrazolium bromide) solution was added to every well and the cells were incubated for another 4 h at 37 °C in 5% CO_2. After the culture medium was removed by MTT solution, 150 μL of DMSO was added to and the resulting solution was shaken for 5 min at room temperature. The optical density (OD) value of the mixture was measured at 490 nm.

2.4 Characterization

Powder XRD patterns were obtained on a Bruker D8 Focus diffractometer using Cu Kα radiation (λ= 0.15406 nm). Scanning electron microscope (SEM) was performed on an FEI Quanta 200 with an acceleration voltage of 25 kV. N_2 adsorption/desorption isotherms were measured at 77 K on a Micromeritics ASAP 2020HD88 instrument. The samples were outgassed at 100 ^oC for 12 h. Total pore volume was taken at P/P_0 = 0.99 single point. The specific surface area was determined by the Brunauer–Emmett–Teller (BET) method. Thermogravimetric analysis (TGA) was carried out on a Perkin–Elmer STA-6000 with a heating rate of 10 ^oC / min in a temperature range from 30 to 800 ^oC under N_2 atmosphere. FT-IR spectra were recorded on a Nicolet 5700 FT-IR spectrophotometer (Thermo-Fisher Scientific, American) using the KBr pellet technique. The photoluminescence (PL) spectra were obtained on an FLS920P Edinburgh Analytical Instrument (Edinburgh Instrument, UK). The UV-vis adsorption spectra were measured on a Perkin-Elmer Lambder 35 spectrophotometer.

3. Results and discussion

3.1 Phase, morphology and structure of hollow $CaWO_4$ microspheres

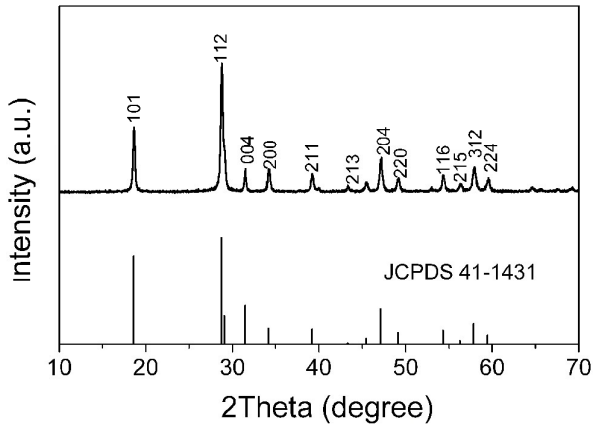

Fig. 1 XRD patterns of hollow $CaWO_4$ microspheres and the standard card of bulk $CaWO_4$ powder.

Fig. 1 shows the XRD patterns of the obtained hollow $CaWO_4$ microspheres. It can be seen that the diffraction peaks can be assigned to the tetragonal phase of $CaWO_4$ (JCPDS No. 41-1431).[32] The strong and sharp diffraction peaks suggest the hollow $CaWO_4$ microspheres are well crystallized. No peaks corresponding to any other phases or impurities were detected, indicating the high purity of hollow $CaWO_4$ microspheres.

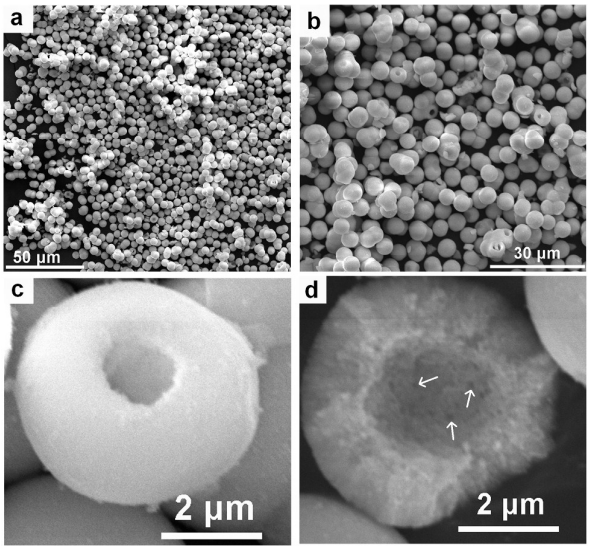

Fig. 2 (a, b) SEM images of hollow $CaWO_4$ microspheres and individual (c) hollow $CaWO_4$ microsphere without and (d) with broken shell.

The morphology of the sample was further characterized by SEM. Fig. 2 displays the SEM images of hollow $CaWO_4$ microspheres. It can be observed that the $CaWO_4$ consists of good dispersed microspheres (Fig. 2a). Some microspheres expose their hollow interiors from the Fig. 2b, implying that the $CaWO_4$ microspheres possess a hollow structure. Fig. 2c shows an individual hollow $CaWO_4$ microsphere with a diameter of about 5 μm. It can be seen that the exterior surface of the microspheres is smooth and the cavity is about 2 μm in diameter. From the SEM image of an individual broken microsphere (Fig. 2d), the interior surface of microsphere is quite rough and existence of some pores (pointed by arrows). The shell is estimated to be about 1.2 μm in thickness. The unique hollow structural $CaWO_4$ microspheres can be employed as drug carriers to load drug molecules.

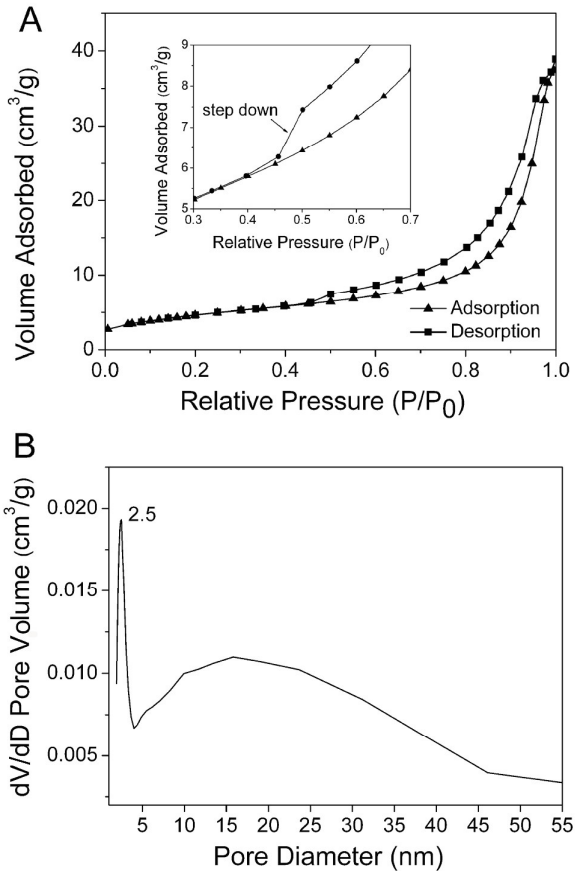

Fig. 3 (A) N_2 adsorption/desorption isotherms and (B) pore size distribution of hollow $CaWO_4$ microspheres. Inset A shows the partial enlarged isotherms in the range of relative pressure from 0.3 to 0.7.

Table 1 Structural parameters and drug loading amount of samples.

Sample	S [a] (m^2/g)	V [b] (cm^3/g)	D [c] (nm)	W [d] (mg/g)
$CaWO_4$	16.4	0.06	2.5/16	-
$CaWO_4$-IBU	12.5	0.04	16	41
T-$CaWO_4$	10.4	0.07	30	-
T-$CaWO_4$-IBU	7.5	0.05	30	44

[a] BET surface area.

[b] Single-point total pore volume at P/P_0=0.99.

[c] Pore size, which was determined by the BJH method from the adsorption branch of the isotherm.

[d] Amount of IBU loaded calculated by TGA, which was defined as the of the loading IBU in the $CaWO_4$ microspheres carriers.

Actually, N_2 adsorption/desorption measurement is an effective tool to investigate the pore structure of porous materials. Fig. 3 depicts the N_2 adsorption/desorption isotherms and pore size distribution of hollow $CaWO_4$ microspheres. From the adsorption branch of nitrogen sorption isotherms (type-IV) is shown in Fig. 3 A, it exhibits that the amount of N_2 adsorbed is small in the low relative pressure and followed by a significant increase at high relative pressure due to the capillary condensation, which is a typical feature of mesoporous materials.[33] Moreover, it is found that the adsorption/desorption hysteresis phenomenon occurred in the relative pressure range of 0.45-1.0, which is associated with the hollow cavity with mesoporous shell.[34-36] Additionally, it should be note from Fig. 3A that the hysteresis loop (type-H3) exhibits a step-down (see inset in Fig. 3A) in the desorption branch associated with the hysteresis loop closure at relative pressure of about 0.45, indicating existence of aggregates of slit-shaped pores.[33, 37] The slit-shaped pores of $CaWO_4$ microspheres were possibly formed by the aggregation of small particles during the growth of $CaWO_4$ microspheres. The pore size distribution calculated from the adsorption branch using BJH method is displayed in Fig. 3B, it can be seen that a sharp distribution at 2.5 nm and a wide distribution in the range of 5-45 nm with a maximum peak of 16 nm are observed, implying that the type of pores with a diameter of 2.5 nm have a majority in the mesopores. As list in Table 1, the total pore volume and BET surface area of hollow $CaWO_4$ microspheres are 0.06 cm^3/g and 16.4 m^2/g, respectively. The above results show that the obtained $CaWO_4$ microspheres possess a hollow structure with mesoporous shell, which make them suitable to be employed as drug carriers.

3.2 Photoluminescent properties of samples

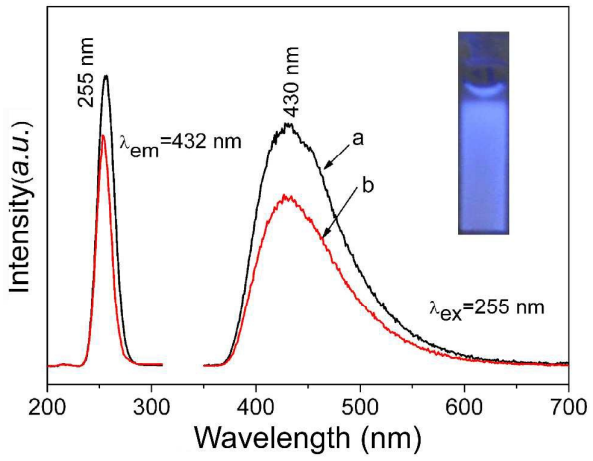

Fig. 4 Excitation (left) and emission (right) spectra of (a) hollow $CaWO_4$ and (b) $CaWO_4$-IBU. The inset is the luminescent photograph of $CaWO_4$-IBU microspheres dispersed in PBS (pH=7.4) buffer under 255 nm irradiation.

Fig. 4 shows the excitation (left) and emission (right) spectra of $CaWO_4$ and $CaWO_4$-IBU. The excitation spectra shows a broad band from 230 to 280 nm with a maximum at 255 nm, which corresponds to the charge transfer transition in WO_4^{2-} groups in which an oxygen (O) 2p electron goes into empty tungsten (W) 5d orbital.[37] The emission spectra of $CaWO_4$ show a broad band and with a maximum at 430 nm upon excitation at 255 nm. Generally, the excitation and emission spectra of $CaWO_4$ is mainly attributed to transitions from the $^1A_1$ ground state to the high vibration level of $^1T_2$ and from the low vibration level of $^1T_2$ to the $^1A_1$ ground state within the WO_4^{2-} complex.[30] Obviously, compared to the blank $CaWO_4$, the $CaWO_4$-IBU sample also exhibits similar emission except for the slightly decrease of intensity (Fig. 4b and inset), suggesting the IBU release process can potentially be tracked by the change intensity of emission.

3.3 Cytotoxicity of $CaWO_4$ microspheres

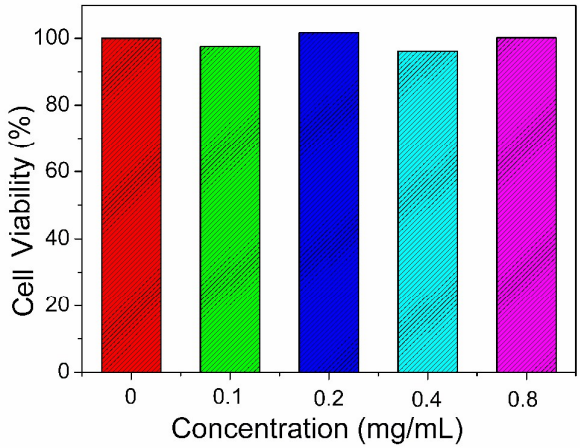

Fig. 5 Cell viability of hMSCs cells incubated with of $CaWO_4$ microspheres for 24 h.

To investigate the cytotoxicity of the hollow $CaWO_4$ microsphere, a MTT assay was performed on hMSCs. As shown in Fig. 5, more than 96.2% of viabilities can be observed over a varying concentration range (from 0.1 to 0.8 mg/mL), indicating that the $CaWO_4$ microspheres have no significant cytotoxic effect on hMSCs. These results indicate that the hollow $CaWO_4$ microspheres have good biocompatibility and might be used as drug carrier in the biomedical fields.

3.4 Interaction between $CaWO_4$ and IBU

Since the interaction between carrier and drug plays an important role in drug loading and releasing process. Thus, it is very necessary to investigate the interaction between $CaWO_4$ carriers and IBU molecules. Fig. 6A shows the FT-IR spectra of samples. As shown in Fig. 6A-a, pure IBU shows a strong band at 1720 cm^{-1}, which corresponds to the C=O group absorption of IBU molecules. For the $CaWO_4$ microspheres (Fig. 6A-d), a strong adsorption band at 803 cm^{-1} and a weak one at 443 cm^{-1} can be observed, which arise from the stretching vibration and bending vibration of the W-O bond, respectively.[37] In the case of the physical mixture of $CaWO_4$ and IBU (Fig. 6A-b), a simple combination of the

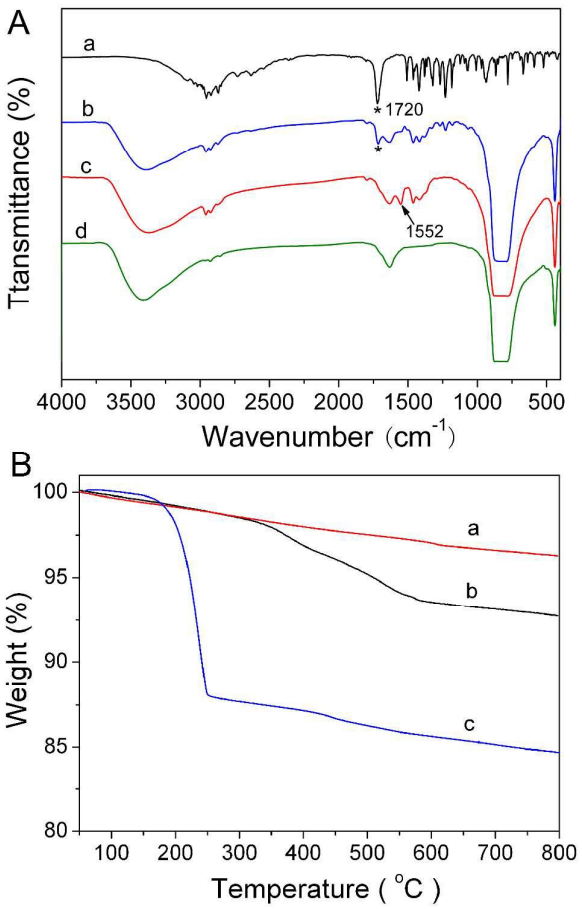

Fig. 6 (A) FT-IR spectra of (a) pure IBU, (b) the physical mixture of $CaWO_4$ and IBU, (c) $CaWO_4$-IBU and (d) $CaWO_4$. (B) TGA curves of (a) $CaWO_4$, (b) $CaWO_4$-IBU, (c) the physical mixture of $CaWO_4$ and IBU.

spectra of $CaWO_4$ (Fig. 6A-d) and IBU (Fig. 6A-a) can be observed, suggesting weaker or no interaction between them when $CaWO_4$ microspheres and IBU molecules were physically mixed. However, after loading of IBU into the $CaWO_4$ (Fig. 6A-c), the C=O band from IBU almost disappeared. Instead, a new strong absorption band at 1552 cm^{-1} is observed, which can be assigned to the asymmetric stretching vibration of $-COO^-$.[38] This observation may be explained by the fact that the transfer of a proton from –COOH of IBU to the WO_4^{2-} of $CaWO_4$, which confirms that the existence of strong interaction between IBU and $CaWO_4$ microspheres.

The interaction between $CaWO_4$ carriers and drug molecules were also investigated by TG analysis. Fig. 6B displays the TGA profiles of samples. For the blank $CaWO_4$ (Fig. 6B-a), only a negligible weight loss (about 3wt%) was found in the range of 100 to 600 °C. The TGA curve of the physical mixture of $CaWO_4$ and IBU (Fig. 6B-c) shows a significant weight loss from about 150 to 250 °C due to pyrolysis of IBU molecules. Compared with the physical mixture of $CaWO_4$ and IBU sample, however, the TGA curve of $CaWO_4$-IBU (Fig. 6B-b) shows a much higher pyrolysis temperature (from about 320 to 550 °C) when IBU molecules were loaded into the hollow $CaWO_4$ microspheres, suggesting the thermal stability of IBU was enhanced because of the interaction between IBU and $CaWO_4$.[39, 40] Obviously, such strong interaction will contribute to delay the drug release.[38]

3.5 Drug loading and release

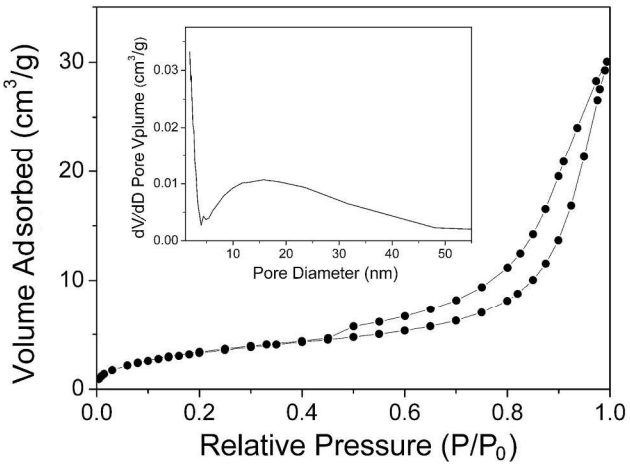

Fig. 7 N_2 adsorption/desorption isotherms and (inset) pore size distribution of $CaWO_4$-IBU microspheres.

To investigate the drug loading and release behavior from hollow $CaWO_4$ microspheres, IBU, a typical anti-inflammatory drug, was chosen as a model drug to be loaded into the $CaWO_4$ microspheres. During the drug loading process, the IBU molecules are entrapped in the inner space of $CaWO_4$ microspheres by an impregnation process. This can be confirmed by N_2 adsorption/desorption measurement. After loading of IBU into $CaWO_4$ microspheres, as shown in Table 1, the BET surface area and the total pore volume of the $CaWO_4$ microspheres decrease from 16.4 to 12.5 m^2/g and 0.06 to 0.04 cm^3/g, respectively, implying that IBU molecules were loaded into inner space of $CaWO_4$ microspheres. What is more, from the pore size distribution of $CaWO_4$-IBU (inset in Fig. 7), we can observe that the sharp distribution at 2.5 nm disappeared compared with the blank $CaWO_4$, implying the mesopores with a diameter of 2.5 nm were almost occupied by IBU molecules. These results further confirm that the IBU molecules were loaded into the cavity and mesopores of hollow $CaWO_4$ microspheres.

The amount of IBU molecules loaded in the carriers can be estimated by TGA. For the porous materials, the morphology and pore texture play a crucial role in the drug loading.[41, 42] Comparatively, as shown in Fig. S1 (ESI†), the hollow T-$CaWO_4$ microspheres (about 5 μm in diameter) also exhibit a hollow structure with mesoporous pores in the shells, which is similar to that of $CaWO_4$ microspheres obtained by a typical procedure in this study. Additionally, type-IV isotherms can be also observed for the T-$CaWO_4$ sample (Fig. S2, (ESI†), indicating they possess a similar pore structure (see Table 1). As shown in Fig. 6B, the amount of IBU loaded in the hollow $CaWO_4$ microspheres obtained by our procedure is calculated to be about 41 mg/g. Comparatively, the content of IBU in T-

$CaWO_4$ microspheres is estimated to be about 44 mg/g (Fig. S3 (ESI†)). The similar amount of drug loaded indirectly indicated that the hollow $CaWO_4$ microspheres synthesized by the template-free hydrothermal process have the similar morphology, pore structures and well drug loaded performance.

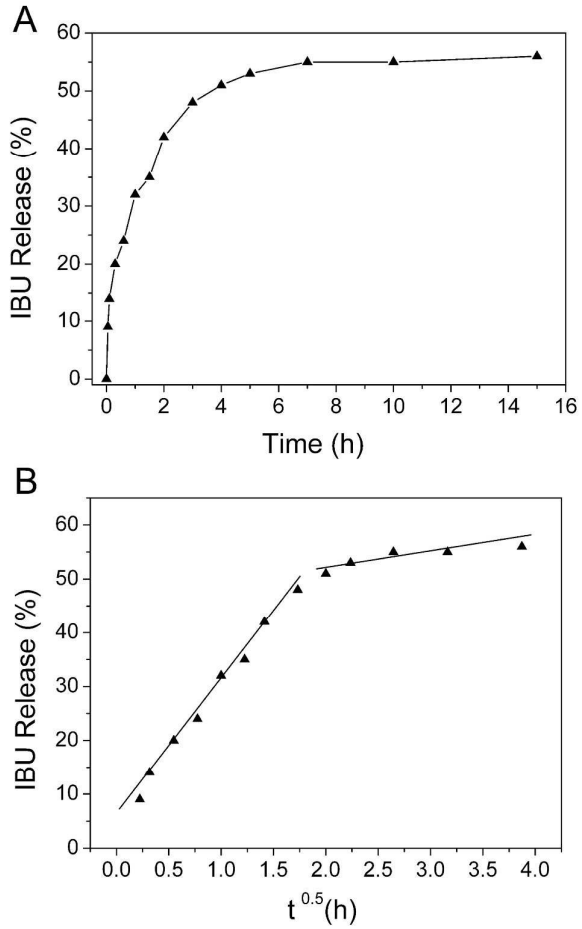

Fig. 8 (A) Cumulative IBU release from $CaWO_4$ microspheres in pH = 7.4 PBS solution. (B) Higuchi square root of time plot for the release of IBU from $CaWO_4$ microspheres.

Fig. 8A depicts the *in vitro* release of IBU from $CaWO_4$ microsphere in pH = 7.4 PBS solution at 37 °C. Obviously, a relatively fast release and then a sustained release behavior can be observed. About 42% drug was released from the carrier in the first initial 2 hours, while only about 13 % IBU molecules were released from 2 to 16 hours. Similarly, as shown in Fig. S4 (ESI†), the IBU molecules released from the T-$CaWO_4$ microspheres also show a fast release during the initial 2 hours and followed by a sustained release. Previous reports showed that the pore geometry has an important influence on the drug release behavior.[43] In this study, two samples exhibit similar pore structure. Thus, such similar IBU release behaviors from $CaWO_4$ and T-$CaWO_4$ may attribute to the similar pore structures of them. This type of drug release behavior would be useful to therapy disease in practical clinic, which usually needs a high dosage in the initial stage and followed by a sustained release with a smaller dose.

To further investigate the drug release behavior from $CaWO_4$ microspheres, the release data are also analyzed by kinetic model. The kinetics of release of drugs from an insoluble, porous carrier material can be described according to the Higuchi model.[44, 45]

$$f = k \cdot t^{0.5}$$

where f is the fractional release of drug, k is the release rate constant and t is time. Thus, for a purely diffusion controlled process, a linear relationship should be observed when small drug molecules, which distributed uniformly throughout the matrix, release from the carrier.[45] From the Higuchi plot presented in Fig. 8B, however, it clearly deviated from the overall linearity. Instead, two straight lines can be observed, corresponding to a two-step mechanism for drug release. In the first step, i.e., the initial fast release stage, it can be explained that some IBU molecules might be physically adsorbed on the pore mouths and exterior surface of $CaWO_4$ microspheres and rapidly diffused into the medium. Whereas in the second-step, i.e., in the case of sustained release stage, some IBU molecules were loaded into the inner surface and mesopores, causing the drug diffusion to be restricted due to the steric hindrance.[46] In addition, the strong interaction (as mentioned in the above section) between IBU molecules and carrier will also reduce the drug release rate.

It is well known that targeted drug delivery systems could directly transport drug molecules to the disease sites and thus can improve therapeutic efficacy and reduce the side effect, which is one of development directions in intelligent drug delivery systems and biomedicine fields. It should be denoted that the hollow $CaWO_4$ microspheres carriers we prepared can not targeted to the specific tissue or organs due to the lack of modification with functional groups or materials on its surface. Thus, the hollow $CaWO_4$ microspheres loaded with drug may transport the drug to the possible tissue or organs (e.g., stomach, small intestine, colon, *etc*.) by oral route In this study, the main concerns that the synthesis, structure analysis, drug loaded performance and release behavior are the fundamental prerequisites to realize targeted drug delivery using the hollow $CaWO_4$ microspheres as carrier. Further work on the modification with functional materials, such as smart polymer, magnetic particles, aptamer, etc., on the surface of $CaWO_4$ microspheres is required in future.

4.Conclusion

In summary, luminescent hollow $CaWO_4$ microspheres with a diameter of about 5 μm were prepared via a facile, template-free hydrothermal route. The resultant $CaWO_4$ microspheres exhibit huge cavity, mesoporous shell, good biocompatibility and brightly blue luminescence, which can be designed as drug carrier to study the drug loading and release properties using IBU as a model drug. The results show that the IBU molecules were indeed loaded into the inner surface and mesopores of hollow $CaWO_4$ microspheres. There exist strong

interaction between IBU molecules and $CaWO_4$ microspheres. The drug release behavior *in vitro* exhibits a two-step release mechanism, i.e., an initial fast release and then a sustained release. We believe this kind of luminescent hollow $CaWO_4$ microspheres have potential application in controlled drug delivery systems.

Acknowledgements

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Luminescent Hollow $CaWO_4$ Microspheres: Template-Free Synthesis, Characterization and Application in Drug Delivery

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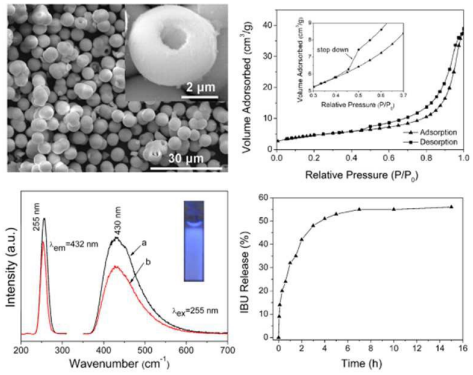
Luminescent hollow structural $CaWO_4$ microspheres with huge cavity and slit-like pores in the mesoporous shells were prepared by a template-free, facile hydrothermal method. The obtained $CaWO_4$ sample shows a strong interaction between drug ibuprofen (IBU) molecules and sustained-release property for IBU.



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