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Size-Control and Surface Modification of Flexible Metal-Organic Framework MIL-53(Fe) by Polyethyleneglycol for 5- Fluorouracil Anticancer Drug Delivery

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The flexible metal-organic frameworks (MOFs) materials, also called soft porous crystals which combine the crystalline order of the underlying coordination network with cooperative structural transformability, have been extensively studied as promising materials for various applications such as sensing, drug delivery, catalysis, host-guest complex etc. Among them MOFs is effectively used as a carrier for drug delivery. Herein, a flexible metal-organic framework MIL-53(Fe) functionalized with polyethyleneglycol (PEG) was successfully fabricated by ultrasonication. The prepared material was characterized by scanning electron microscopy (SEM), X-ray diffraction (XRD), transmittance electron microscopy (TEM), Brunauer-Emmett-Teller (BET) surface area and infrared spectroscopy (IR). The effect of the PEG content on the morphology and particles size of the MIL-53 was investigated in detail. The resultant flexible MIL-53(Fe)-PEG materials were seen to be homogeneous with the morphology of hexagonal bipyramidal structure, approximately 700 nm in length and 400 nm in diameter. Furthermore, we investigated loading of 5-fluorouracil (5-FU) drug and its release in vitro conditions by employing MIL-53(Fe)-PEG. The results showed that in vitro condition, only 31% of the drug released after 3 h, and released completely after approximately 6 days. Thus, we believe that use of MIL-53(Fe)-PEG may overcome current issue of sustain release.

Introduction

In the last few decades, metal-organic frameworks (MOFs), which were constructed from the organic ligands and metallic ions, have been attracted tremendous attention of reseachers due to their high surface area, porous tunability and chemical properties.[1] The MOFs materials could be employed in many potential applications such as gas storage and separation, catalysis, drug delivery, fuel cells, solar cells, sensors and electronic devices to name few.[2] In the field of biomedicine application as drug delivery/imaging agents, well-defined porous MOFs materials are very crucial.[3] In order to employ porous MOFs as drug carriers, the materials have to meet the following properties: water dispersibility and stability,[4] particle size of less than 200 nm„[4–5] biodegradability and compatibility,[6] controllable pore size and controllable composition and functionalization of the surface.[7] The flexibible MOF materials is in solid-state, which can involve atomic displacement of several Ångströms while maintain the atomic-scale connectivity and crystallinity of the structure.[8] One if the most well-studied flexible MOF material is the MIL-53.[9]

Of the properties of MOFs in biomedical applications, the particle size is particularly important for administrative purpose and incorporating MOFs with other compounds and/or materials. Many different methods such as conventional hydrosolvothermal,[4,10] reverse-phase microemulsions,[11] interfacial,[12] sonochemical,[10a,13] and microwave-assisted syntheses,[4,10a, 11b, 14] and spray drying,[15] have been employed to fabricate the stable, well-defined and monodisperse MOFs materials. In the last decade, ultrasonication method has been attracted much attention as an effective approach for controlling of the nucleation and crystallization process. Ultrasound irradiation has been proved to be a feasible mixing method and it can intensify mass transfer and accelerate molecular diffusion. The coordination modulation method has been also used to precisely control the particle size. Importantly, the control of the pore volume and the process of crystal growth of the MOF materials was done by introducing the monovalent capping ligands such as polyethyleneglycol (PEG). In 2008, Horcajada *et al.* synthesized MIL-53(Fe) (one of the flexible MOF) and used as an adsorbent for gases adsoprtion and a carrier for in vitro ibuprofen delivery.[16] The resultant MIL (53) MOF showed high adsorption capacity of 0.21 g ibuprofen/g MOF. Importantly, ibuprofen-loaded MIL (53) revealed a very slow delivery of ibuprofen in simulated body fluid at 37 °C, to

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complete release of ibuprofen took more than three weeks. This slow release was ascribed to the framework flexibility of the MIL(53), which maximize the bonding interaction while still keeping the steric hindrance. However, the pore sizes of these MOFs was only suitable for incorporating the relatively drug molecules (for example, ibuprofen), which limit their application as drug carrier. Furthermore, the monovalent capping ligands (PEG) haven't been used to modify the surface of MIL-53(Fe).

Therefore, the surface modification and size control of the microporous MOFs are essential requirement to use these MOFs as drug delivery systems for drug molecules such as 5-fluorouracil (5-FU) (Figure S1), as 5-FU is one of the drug largely used for two types of cancers treatment[17] such as malignancies like glioblastoma[18] and breast cancer.[19]

Herein, we have proposed a simple approach to fabricate the flexible MIL(53) with assistance of polyethyleneglycol (PEG) using ultrasonication method. By using the PEG, the particle and their pore size of the MIL(53) are precisely controlled, which shown to be suitable for incorporating 5-FU and their sustain release. TEM, SEM, BET and XRD were used to characterize the prepared MOF. The loading and release of 5-FU by the resultant MIL(53) are determined.

Results and Discussion

Figure 1 illustrates the XRD patterns of prepared MIL-53 with and without the assistance of PEG. The main diffraction peaks

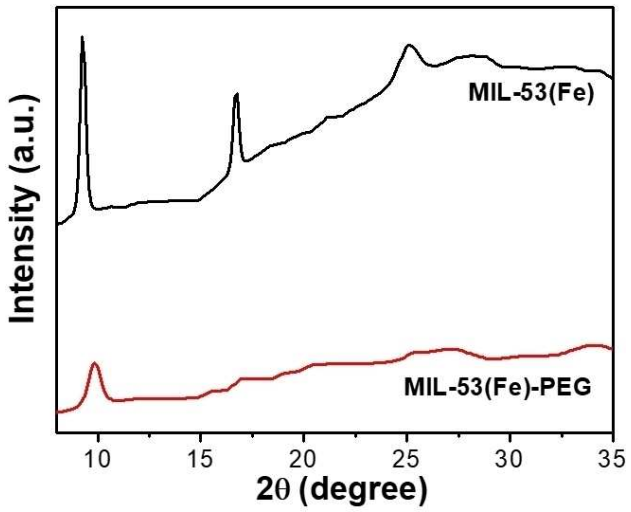

Figure 1. XRD pattern of flexible MIL-53(Fe) synthesized by ultrasonic for 20 min at 75% power without (black curve) and with (red curve) PEG assistance

of MIL-53 and MIL-53(Fe)-PEG are at 9.25, 16.75, 25,05 and 9.85, respectively, which are in good agreement with diffraction peaks of MIL-53 reported in previous works.[20] This result confirms that the obtained materials is MIL-53(Fe) crystalline structure with the monoclinic symmetry (*C*2/*c*, No. 15).[16]

The IR spectroscopy was employed to understand thoroughly functional groups and molecular structure of the flexible MIL-53(Fe)-PEG material. Figure 2 shows the IR spectra

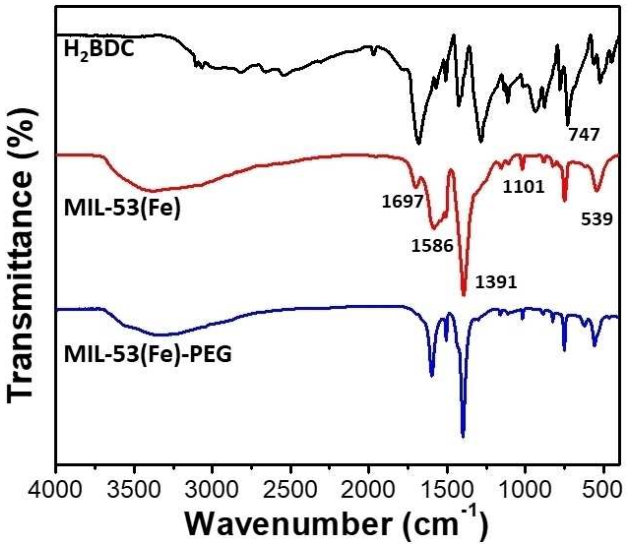

Figure 2. IR spectra of H_2BDC compound (black curve), MIL-53(Fe) (red curve) and the flexible MIL-53(Fe)-PEG (blue curve).

of H_2BDC (black curve) and MIL-53(Fe)-PEG (red curve). The broad band observed at around 3000 cm^{-1} in the FTIR spectrum of H_2BDC is the characteristic region of COOH group. In the IR spectrum of the resultant MIL-53(Fe)-PEG, the characteristic peaks in the region of 1400–1700 cm^{-1} are denoted to the typical vibrational bands of the carboxylic acid function. While the absorption band of carbonyl groups in the H_2BDC is observed at 1697 cm^{-1}, the stretching vibration of the carboxyl groups in the ligand with the Fe(III) centers appears at 1586 cm^{-1}.[21] The low intensity of the peak at 1967 cm^{-1} is also visible in the MIL-53(Fe)-PEG IR spectrum, which demonstrates that the free H_2BDC ligand presences in the obtained MOF material. The absorption band at 747 cm^{-1} is attributed to the C–H bonding vibration of the benzene rings.[22] Moreover, the –C–O-C- bonding vibration in PEG was evident by the appearance of a characteristic peak at about 1101 cm^{-1}.[23] The presence of a stretching at 539 cm^{-1} is ascribed to the Fe–O bonding, which form between carboxylic groups of the H_2BDC and Fe(III) metals.[21,24]

The morphologies of the synthesized flexible MIL-53 and MIL-53(Fe)-PEG were investigated by using Scanning Electron Microscopy (SEM) as shown in Figure 3. Under synthesizing condition without PEG, the MIL-53 form irregular "inhaled" octahedron crystals with average diameter of 500 nm (Figure 3a). Interestingly, under the assistance of PEG, the prepared MIL-53(Fe)-PEG are small, well-distributed and homogeneous with the morphology of hexagonal bipyramidal structure, approximately 700 nm in length and 400 nm in diameter (Figure 3b). This indicates that PEG has significantly affected to the shape of MIL-53 and confirms the successful functionalization of the surface of MIL-53 with PEG capping.

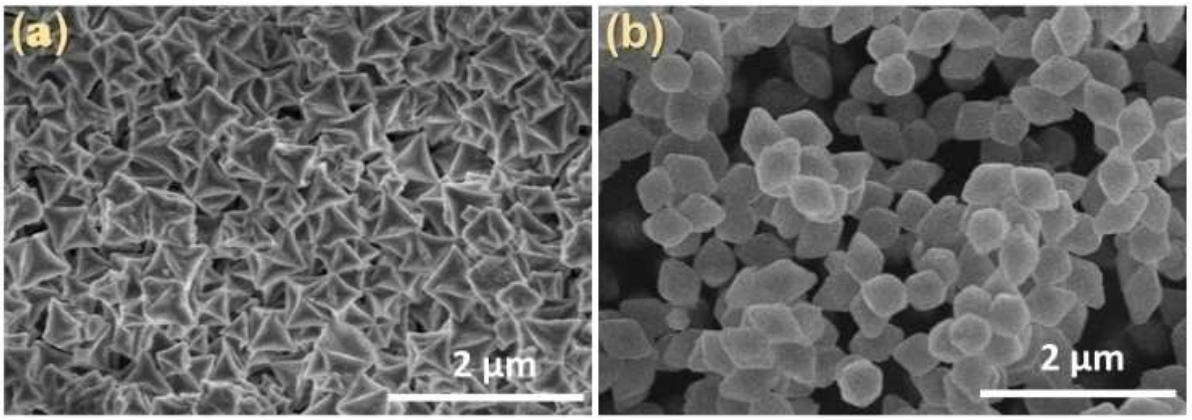

Figure 3. SEM images of flexible MIL-53 prepared by using ultrasonic in 20 minutes (A) without and (B) with the PEG assistance (PEG content of 20 ml).

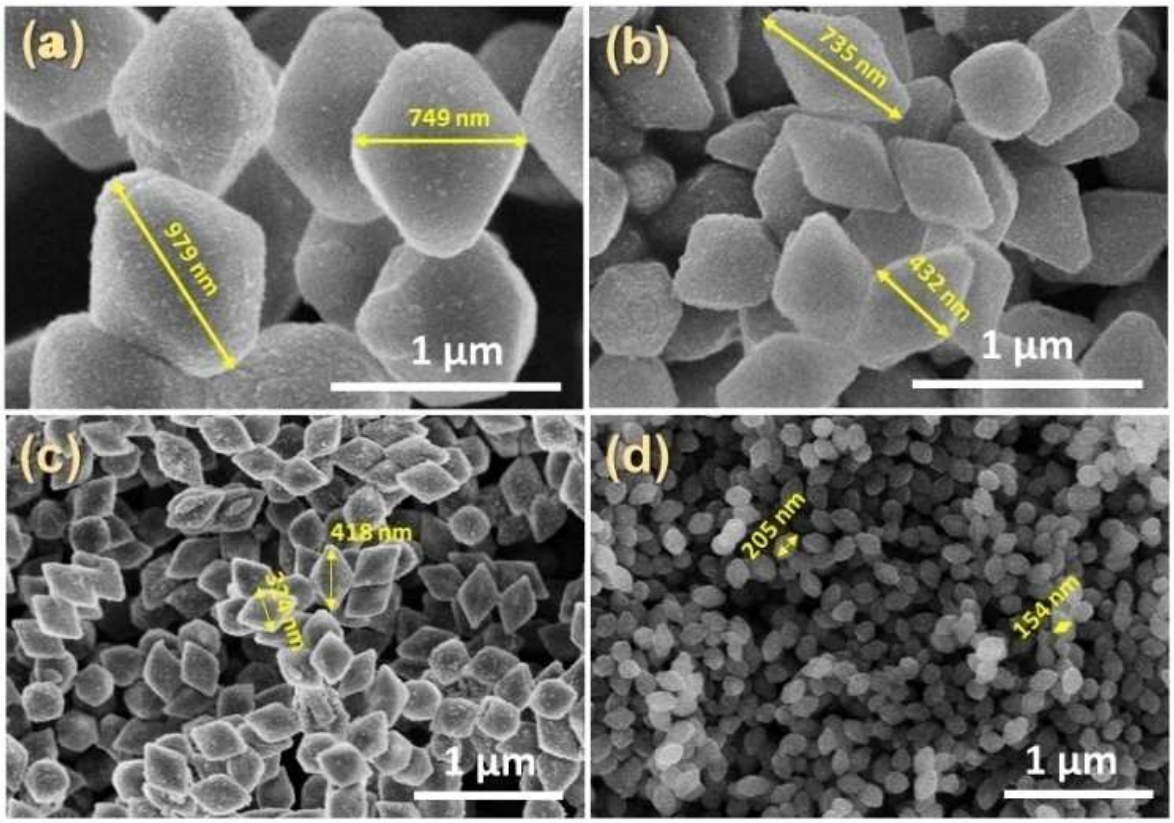

Figure 4. SEM images of flexible MIL-53 fabricated by using ultrasonic in 20 minutes with the PEG volumes of (A) 10 ml, (B) 20 ml, (C) 40 ml, and (D) 60 ml, respectively.

The effect of the PEG concentration on the crystal sizes of MIL-53 was investigated by using SEM images. Figure 4 shows the morphologies of the MIL-53(Fe)-PEG synthesized from different PEG concentrations. It is obvious that the concentration of PEG greatly affects to the crystal sizes of the prepared MIL-53. At PEG volume of 10 ml, a large hexagonal bi-pyramidal structure with the length of about 979 nm and the diameter of 749 nm is observed. Further addition of PEG witnesses a significant decrease in size of MIL-53 crystals with dimension of 735, 418 and 205 nm in length, and 432, 324, and 154 nm in diameter for 20, 40 and 60 ml of PEG, respectively. However, the morphology of MIL-53 remains hexagonal structure in all concentrations of PEG. When the PEG volume is higher than 60 ml, the crystal size and pore size of MIL-53 is too small so that it is not suitable for the purpose of drug carrier. These reduced crystal sizes upon increase of PEG concentration can be explained by effects of PEG during nucleation of MIL-53 as the hydroxyl bonding of the PEG on the surface of MIL-53

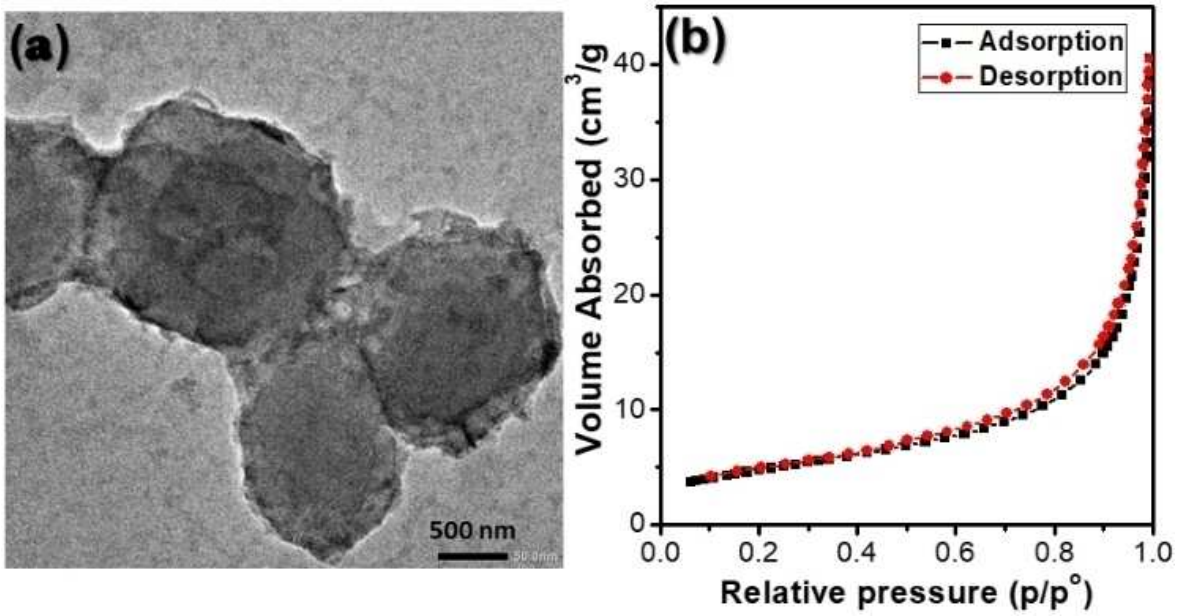

Figure 5. TEM images (a) and nitrogen adsorption-desorption plot (b) of the flexible MIL-53(Fe)-PEG crystals prepared with ultrasonic 75% power for 20 minutes and the PEG volume of 60 ml.

nucleation, which controls the growth of the crystals. At low concentration of PEG, few nucleation of crystals was generated, which lead to the formation of large structure of the MIL-53 crystals. Further increase of the PEG concentration witnessed the formation of more MIL-53 nucleation, as a result the sizes of the obtained MIL-53 crystals were significantly decreased. These results indicate that the PEG can be used to effectively controls the size and modify the surface of the flexible MIL-53 crystals.

In order to further understanding of the surface morphology of MIL-53(Fe)-PEG, TEM image was obtained as shown in Figure 5. It is obvious that TEM image clearly support the formation of MIL-53(Fe)-PEG hexagonal bipyramidal structure with the diameter of around 150 nm and the length of approximately 200 nm, which is consistent with the SEM images (Figure 4d). The Brunauer–Emmett–Teller (BET) multi-point and single-point methods were employed to calculate the total surface area of MIL-53 and MIL-53(Fe)-PEG nano crystals using the N_2 adsorption/desorption isotherm data. Kelvin equation and BJH method were used to determine the pore size and pore volume, respectively. Figure 5b and S2 exhibits the isotherm plot of N_2 adsorption/desorption by the MIL materials and the surface area parameters are summarized in Table 1. The calculated BET surface areas of MIL-53 and MIL-53(Fe)-PEG are 35 and 40.85 m^2/g, respectively. This increased surface area of MIL-53(Fe)-PEG in comparison with MIL-53 crystals is ascribed to the functionalized modification of PEG on the surface of MIL-53 which reduces the size of the crystals and increases the surface area. This incorporation of PEG in the MIL-53 network is also responsible for reducing the pore volume and pore size of MIL-53 crystals from 0.213 cm^3/g and 31 nm in MIL-53 to 0.072 cm^3/g and 7.22 nm in MIL-53(Fe)-PEG, respectively. This pore size is suitable for incorporating and delivering the 5-FU drug.[25]

Table 1. BET surface area values of MIL-53(Fe) prepared without and with the assistance of 60 ml PEG.

Material	Surface area (m^2/g)	Pore volume (cm^3/g)	Pore size (nm)
MIL-53(Fe)	35	0.213	31
MIL-53(Fe)-PEG	40.85	0.072	7.22

5-fluorouracil (5-FU) has been widely employed as drug for treatment of cancers such as anal, breast, colorectal, oesophageal, stomach, pancreatic, and skin cancers. With the suitable particle size and the accessible porosity, the MIL-53 can be used as carrier for 5-FU loading and release. Figure 6a shows the XRD pattern of 5-FU loaded MIL-53(Fe)-PEG, which indicates that the crystalline structure of MIL-53(Fe)-PEG was unchanged after loading 5-FU. The FTIR spectrum of 5-FU encapsulated MIL-53(fe)-PEG is shown in figure 6b. Beside the presences of characteristic peaks of MIL-53(Fe)-PEG mentioned above, the appearance of a peak at ~744 cm-1 corresponding to the C–H out of plane vibration of CF=CH. The strong stretching of the O–H at 3436 cm^{-1} is also observed. The morphology of the 5-FU load MIL-53(Fe)-PEG is shown in Figure 6d, which have the similar morphology to the flexible MIL-53(Fe)-PEG (Figure 6c).

The maximal loading capacity of MIL-53(Fe)-PEG toward 5-FU was determined by immerse the materials in DMF solution containing 5-FU for 10 days. The 5-FU loading capacity was calculated to be 524.326 mg/g MIL-53(Fe)-PEG, which is 52.4% wt 5-FU loading capacity. This 5-FU loading capacity is higher than a zinc metalorganic framework reported previously.[26]

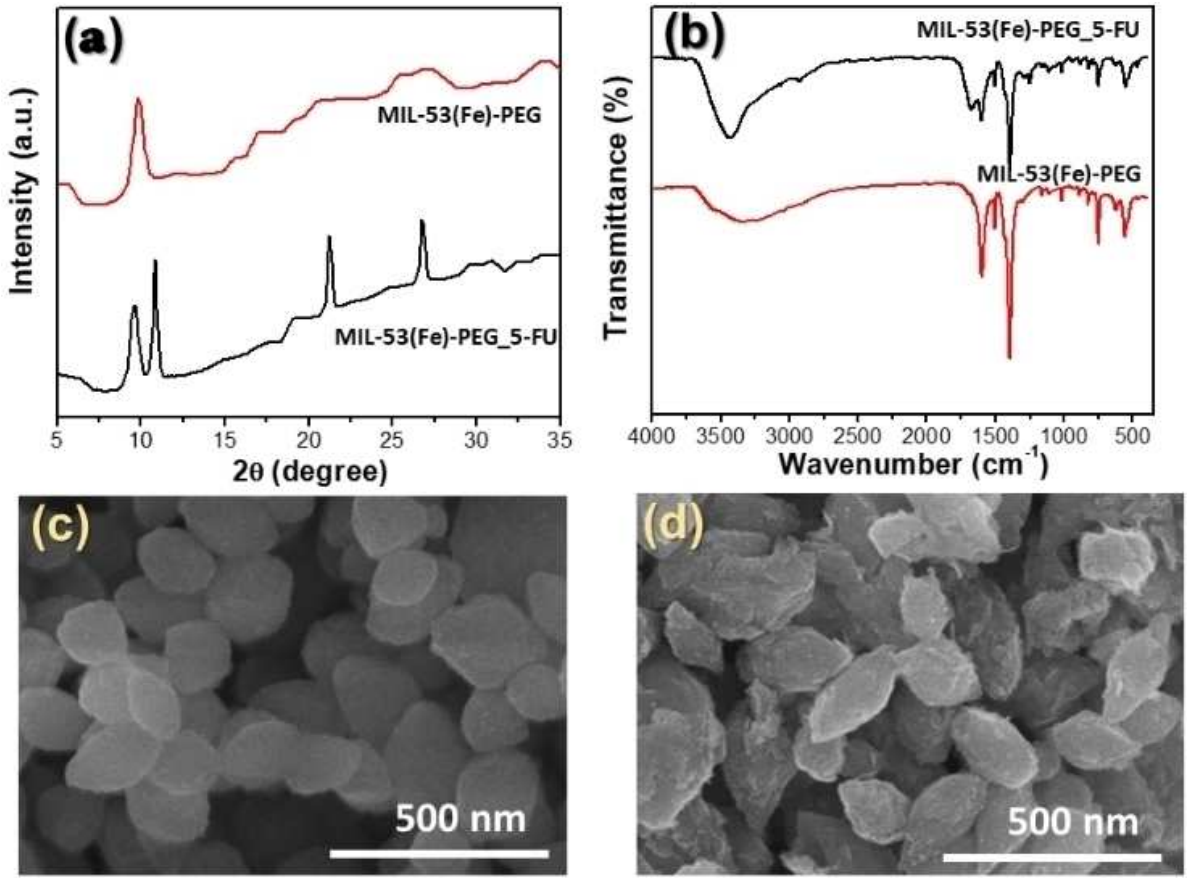

Figure 6. (a) XRD pattern and (b) FTIR spectrum of 5-FU-loaded MIL-53(Fe)-PEG and MIL-53(Fe)-PEG, SEM image of (c) MIL-53(Fe)-PEG and (d) SEM 5-FU-loaded MIL-53(Fe)-PEG.

The in vitro release of 5-FU from the drug loaded MIL-53(Fe)-PEG was investigated as shown in Figure 7. Generally, two step drug releasing stages are commonly observed in MOF drug delivery systems. First stage is the rapid release of the drug in the free form, which is weakly interacted with the MOF materials and the later is ascribed to the slow release of drug with strong bond within the MOF network. Unlike in other MOF materials for drug delivery, the first stage usually occurs very quickly, which exceeded 90% only after 30 minutes of dissolution time.[27] In this case, only 6% of the 5-FU was dissolved after 30 minutes and approximately 31% of the 5-FU was released from the MIL-53(Fe)-PEG in the later 3 hours. This is attributed to strong host–guest interactions of the 5-FU with flexible MIL-53(Fe)-PEG porous framework, which was demonstrated by the sustain release of the 5-FU from the drug-loaded MIL-53(Fe)-PEG materials in the second stage. In this stage, the dissolution of the drug is more slowly with the releasing percentage of 61.2% after 15 hours and reached 83.7% after 78 hours of dissolution time. A complete dissolution of 5-FU occurred after 6 days of immersing time.

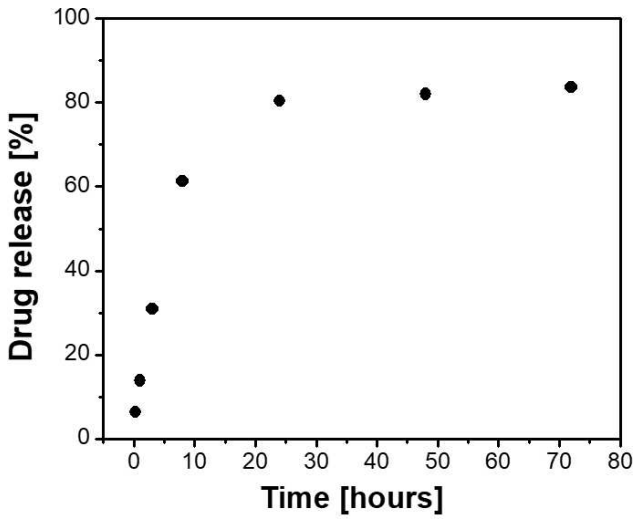

Figure 7. Release profile of 5-FU from MIL-53(Fe)-PEG

Conclusions

In summary, we have successfully fabricated well-defined flexible MOFs of MIL-53(Fe) by using ultrasonication with the assistance of polyethyleneglycol. The flexible MIL-53(Fe)-PEG

materials obtained with condition of ultrasonic 75% power for 20 minutes and the PEG volume of 60 ml are small, well-distribution and homogeneous with the morphology of hexagonal bipyramidal structure, approximately 205 nm in length and 154 nm in diameter. Functionalized modification of PEG on the surface of MIL-53 also reduces the size of the MIL-53 crystals, therefore increases the surface area of the materials from 35 to 40.85 m^2/g. The obtained MOF revealed high uptake of 5-FU drug and importantly, significantly slow release of the drug under in vitro conditions, which is only 31% of the drug released after 3 hours. The complete release of the 5-FU was observed after 6 days of dissolution time. This high loading and slow release of the cancer drugs from MIL-53(Fe)-PEG materials will enable this material as a promising carrier for effective delivery of drugs for cancer treatment in practical.

Supporting information summary

This provides further information about the experimental detail, the structure of 5-Fluorouraci and Nitrogen adsorption-desorption plot of the MIL-53. This material is available free of charge via the internet.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: metal-organic frameworks, MIL-53, flexible MOFs, drug delivery, 5-fluorouracil

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