Controlled uptake and release of imatinib from ultrasound nanoparticles $\text{Cu}_3(\text{BTC})_2$ metal–organic framework in comparison with bulk structure

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Abstract

The porosity of metal–organic frameworks (MOFs) is an important point concerning the possible use of such functional materials for different purposes. In this work, we study uptake and release properties of imatinib (**IM**) from nano Cu(II)-MOF in comparison with bulk Cu(II)-MOF. To explore the absorption ability of the Cu(II)-MOF to **IM**, fresh sample of $\text{Cu}_3(\text{BTC})_2$ was immersed in an aqueous solution of **IM** and were monitored in real time with UV/vis spectroscopy. Results show that the adsorbed quantity of **IM** over nano $\text{Cu}_3(\text{BTC})_2$ (**I**) is much higher than those over a bulk $\text{Cu}_3(\text{BTC})_2$ (**II**).

Keywords: Nanoparticles; Imatinib; Ultrasound; Metal–organic frameworks.

1. Introduction

The field of metal-organic frameworks (MOFs), which are also called porous

coordination polymers (PCPs), has been growing tremendously over the last two decades [1,2]. This fascinating class of crystalline hybrid materials, which are formed by association of metal centers or clusters linked by organic moieties, offer an unique chemical versatility combined with a designable framework and an unprecedentedly large and permanent porosity [3-5]. These materials have enormous potential for many practical structure-related applications. This includes the more traditional areas of storage, separation or controlled release of gases, catalysis, sensing, and drug delivery, as well as the adsorptive removal of hazardous materials, which are based on the pore size and shape as well as the host–guest interactions involved [6-11]. However, the majority of these applications are based on the ability of MOFs to behave as hosts for certain molecules. MOFs have already been tested as microporous materials with exceptionally high porosity, uniform but tunable pore size, and with well-defined molecular adsorption sites [12].

In the present work, we study uptake and release properties of imatinib (**IM**) from $\text{Cu}_3(\text{BTC})_2$ MOF in comparison with activated carbon. **IM** is used to treat certain types of leukemia and other cancers of the blood cells. Imatinib is also used to treat dermatofibrosarcoma protuberans when the tumor cannot be removed surgically, has spread to other parts of the body, or has come back after surgery. Imatinib is in a class of medications called kinase inhibitors. It works by blocking the action of the abnormal protein that signals cancer cells to multiply. This helps stop the spread of cancer cells. $\text{Cu}_3(\text{BTC})_2$ (BTC = 1,3,5-benzenetricarboxylate), also known as HKUST-1, is one of the most recognized MOF with square-shaped pores (9 Å by 9 Å), which for the first time was reported by Williams and co-workers in 1999 [13]. $\text{Cu}_3(\text{BTC})_2$ is a neutral coordination polymer composed of dimeric cupric tetracarboxylate units. Twelve carboxylate oxygen atoms from the two BTC ligands bind to four coordination sites for each of the three Cu(II) ions. This material has enormous potential for many practical structure-related

applications.

2. Experimental section

2.1. Materials and methods

All reagents and solvents were used as supplied by Merck Chemical Company and used without further purification. X-ray powder diffraction (XRPD) was carried out using Philips X'pert diffractometer with monochromatic Cu K α radiation. The simulated XRD powder pattern based on single crystal data were prepared using Mercury software [14]. The samples were characterized with a scanning electron microscope (SEM, Philips XL 30 and S-4160) with gold coating. Ultrasonic generation was carried out using EURONDA (continuous mode, output power: 350 W). Ultrasonic generators have water circulation system and double jacketed vessel. *In situ* UV/vis spectrum experiment has been carried out on a PG Instruments, T80 + UV/vis/NIR spectrophotometer within the wavelength range 190–800 nm, using the same solvent in the examined solution as a blank. Infrared spectra were taken with a FT-IR Bruker, vector 22 spectrometer using KBr pellets in the 400–4000 cm⁻¹ range.

2.2. Synthesis of nano Cu₃(BTC)₂ (I)

In this paper, nano-particles of Cu₃(BTC)₂ were prepared by reaction between Cu(OAc)₂·H₂O and H₃BTC precursors with the molar ratio of 1.8:1.0 under ultrasound irradiation [15]. Cu(OAc)₂·H₂O and H₃BTC separately dissolved in water and ethanol. The Cu(II) solution was added dropwise to H₃BTC solution under ultrasound power. At the end of the sonication process, the product was washed with fresh DMF (3 × 20 mL) and was dried *in vacuo*. For the characterization of the products, scanning electron microscopy (SEM) and powder XRD were used. The nano product was obtained in a

89.0% yield.

2.3. Synthesis of bulk $\text{Cu}_3(\text{BTC})_2$ (**II**)

$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.359 g, 1.8 mmol) and H_3BTC (0.210 g, 1.0 mmol) were dissolved in 12 ml water and ethanol. The mixture was placed in a reactor and heated at 80 °C for 24 h. The resulting blue solid was washed with fresh DMF (3×20 mL). The bulk product was obtained in a 71.3% yield.

3. Results and discussion

3.1. Ultrasound effects

In order to investigate the role of sonicating on the nature of products, compound **II** was performed without ultrasound irradiation. The average particle size for ultrasound method is around 39.5 nm while, the average particle size for sample **II** in similar conditions is over 60.2 nm (Figure 1). Results show that in present of ultrasound radiation, particle sizes are in a low range. This finding has already been observed in other studies on ultrasound-assisted synthesis of nano-particles [15-16]. The growth of nanoparticles by using sonicating is essentially by two processes; one is the diffusion process of the reactants to the surface of the growing crystallite, while the second one is the reaction at the surface of the crystallite to incorporate the reactant as a part of the growth process. In these conditions, the growth proceeds through the new nucleations and increasing the number of particles [17,18].

Suggested position for Fig. 1

3.2. Adsorption affinity

For augment of porosity in $\text{Cu}_3(\text{BTC})_2$, we successfully tested its porosity with

imatinib (guest molecules) by suspending it in an aqueous solution of **IM**. The guest content was estimated by UV/vis spectroscopy (Figure 2 and Table 1). The change of intensity and width indicates that the resulting solid $\text{Cu}_3(\text{BTC})_2$ retains the host framework crystallinity as **IM** molecules diffused in [19]. To explore the absorption ability of the $\text{Cu}_3(\text{BTC})_2$ to imatinib, fresh sample of $\text{Cu}_3(\text{BTC})_2$ (13.0 mg) was immersed in an aqueous (50.0 mL) solution of **IM** (0.17 mmol) and were monitored in real time with UV/vis spectroscopy.

Suggested position for Fig. 2

Adsorption of guest was spontaneous and endothermic, and the entropy increases with the adsorption of guest. Entropic hydrophobic interactions occur when a guest replaces the water within a cavity. An increase in entropy increases the favorability of the process. The adsorption of **IM** by $\text{Cu}_3(\text{BTC})_2$ is likely dominated by hydrogen bonding to the SBU, and subsequently to other **IM** molecules, as there is no change in the MOF due to covalent bonding with **IM**, as evident in the FT-IR spectrum (Figure 3).

Suggested position for Fig. 3

The sorption capacity of $\text{Cu}_3(\text{BTC})_2$ increases with the increase of contact time. As shown in Figure 2, the adsorbed quantity of **IM** over **I** is much higher than those over an activated carbon and **II**. In comparison as long as 144 h, the uptake of **IM** (96.93%) on **I** is remarkable and clearly exceeds that of **II** (81.12%) and activated carbon (34.03%) in the aqueous solution of **IM**. In nano $\text{Cu}_3(\text{BTC})_2$ and all of the nano-MOFs the channel length is decreased so that the amount of adsorption is increased a little [20, 21]. The uptake of **IM** in solution increases linearly with time, indicating that the **IM** Adsorption is governed by the host-guest interaction.

3.3. Release assays

The encapsulated guest could be easily removed from the network upon immersion of guest@MOFs in organic solvents. To further investigate the kinetics of the guest delivery of the framework, UV/vis spectra were recorded at room temperature. The temporal evolution UV/vis spectrum for **IM** in ethanol solution becomes stronger with increasing **IM** content (Figure 4). The delivery of **IM** in ethanol increases with time, indicating that the **IM** release is governed by the host-guest interaction. Once these interactions fade out with increasing **IM** extrusion, the delivery in the second stage is mainly governed by a free diffusion process, and a complete **IM** release from **I** needs more than 10 days to attain the equilibrium state. The two parameters, the maximum **IM** content and the rate, suggest that they may be due to a free diffusion process in the absence of well-defined host-guest interactions. It seems that in **I** the length of channel become smaller and the **IM** molecules are more stable than **II**. As a result, the delivery of **IM** from **II** can be faster than **I**. A summary of the different treatments is provided in Table 1.

Suggested position for Figs. 4

3.4. X-ray powder diffraction (XRPD)

To determine the crystal phase of Cu(II)-MOF (**I** and **II**), X-ray powder diffraction (XRPD) measurements were carried out over the diffraction angle (2θ) of 5-50°. These copper-benzenecarboxylate units form a face-centered crystal lattice of *Fm3m* symmetry, which has a complex three-dimensional channel system as depicted in Figure 5. The main pores of ca. 0.9 nm in diameter form a cubic network that is well seen from the [100] direction. Planar C₃H₆(O₂C)₃ segments form tetrahedron shaped side pockets is shown in Figure 5A. The window of these pockets is ca. 0.35 nm in diameter, which is wide enough for small molecules of gases to pass through, but it is too tight for larger organic

molecules [22]. In MOF $\text{Cu}_3(\text{BTC})_2$, the triangular shaped coordination of the BTC^{3-} ligand plays an important role in the linkage of the nodes resulting in a three-dimensional honeycomb framework (Figure 5B). $\text{Cu}_3(\text{BTC})_2$ is also based on a binuclear Cu(II) unit, in which Cu(II) centers are coordinated to four carboxylate oxygen atoms from two fully deprotonated BTC^{3-} ligands, and one oxygen atom from the H_2O ligand (Figure 5C). The distance between two Cu#1 centers is 2.628 Å.

Suggested position for Figs. 5

Figure 6 shows the XRPD patterns; simulated from single crystal X-ray data of $\text{Cu}_3(\text{BTC})_2$ (A), as-synthesized $\text{Cu}_3(\text{BTC})_2$ (B), and $\text{Cu}_3(\text{BTC})_2$ soaked in an aqueous solution (10^{-4} mol L^{-1}) of **IM** (**IM**@ $\text{Cu}_3(\text{BTC})_2$) at room temperature for 24 h (C). The six major peaks found at 11.51, 13.5, 13.51, 17.5, 19.0, 20.4 and 25.9° on the 2 theta scale correspond respectively to the (222), (400), (511), (440), (442) and (731) crystal planes. Acceptable matches, with slight different in 2θ , were observed between the simulated from single-crystal X-ray data patterns and those from the experimental powder X-ray diffraction patterns of **IM**@ $\text{Cu}_3(\text{BTC})_2$.

Suggested position for Fig. 6

Thermal decomposition of the nano-particles of $\text{Cu}_3(\text{BTC})_2$ at 540 °C for 12 hours in static atmosphere of air result in formation of CuO micro-structures, as established by its powder XRD pattern (Figure 7). The obtained pattern match with the standard pattern of monoclinic CuO, space groups $C2/c$ with the lattice parameters $a = 4.684$ Å, $b = 3.425$ Å, $c = 5.129$ Å and $z = 4$ (JCPDS card file No. 05-0661).

Suggested position for Fig. 7

4. Conclusions

$\text{Cu}_3(\text{BTC})_2$ metal–organic frameworks (Cu(II)-MOF) were prepared by ultrasound

technique. $\text{Cu}_3(\text{BTC})_2$ MOF may indeed is suitable for applications requiring frequent loading and unloading of guests. The activated empty phase has excellent and promising imatinib affinity, and it can be slowly delivered to ethanol controllably. Results suggest that the adsorbed quantity of imatinib over nano Cu(II)-MOF is much higher than those over a bulk Cu(II)-MOF. To verify the crystalline nature of the product, the XRPD patterns of the resulting product were investigated. From XRPD, it is clearly confirmed that the Cu(II)-MOF particles were successfully prepared by the ultrasound irradiation method.

Acknowledgements

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Figures:

Figure 1. SEM photograph and the corresponding particle size distribution histogram of compounds **I** and **II**.

Figure 2. Temporal evolution of UV/vis absorption spectra for the loading of **IM** from compounds **I** (A), **II** (B) and activated carbon (C). The amount of **IM** absorption from nano $\text{Cu}_3(\text{BTC})_2$ in comparison with bulk $\text{Cu}_3(\text{BTC})_2$ and activated carbon (D).

Figure 3. FT-IR spectra of H_3BTC , **IM**@nano $\text{Cu}_3(\text{BTC})_2$ at room temperature for 24 h, nano $\text{Cu}_3(\text{BTC})_2$ and bulk $\text{Cu}_3(\text{BTC})_2$.

Figure 4. Temporal evolution of UV/vis absorption spectra for the delivery of **IM** from compounds **I** (A) and **II** (B). The amount of **IM** release from nano $\text{Cu}_3(\text{BTC})_2$ in comparison with bulk $\text{Cu}_3(\text{BTC})_2$ (C).

Figure 5. View from a direction close to [111] shows the tetrahedron-shaped side pockets with triangular windows of internal diameter of 0.35 nm. The windows of the pockets are open to the main channels (A). The pores of $\text{Cu}_3(\text{BTC})_2$, hydrogen atoms are omitted for clarity (B). Binuclear Cu_2 cluster (O: red; C: grey; and Cu: yellow) (C).

Figure 6. Simulated pattern based on single crystal data of XRPD pattern of $\text{Cu}_3(\text{BTC})_2$ (A), compound **I** (B), compound **II** (C), XRPD patterns of compound **I** soaked in an aqueous solution of **IM** at room temperature for 24 h.

Figure 7. XRPD pattern of the CuO particles after calcinations) (A). SEM photographs and corresponding wavelength-dispersive X-ray (WDX) analysis of CuO (B).

Figure 1.

Figure 2 (Continued).

Figure 2.

Figure 3.

Figure 4.

Figure 5.

Figure 6.

A **B**

Figure 7.

Table 1. The amount of **IM** absorption/release from nano $\text{Cu}_3(\text{BTC})_2$ in comparison with bulk $\text{Cu}_3(\text{BTC})_2$ and activated carbon.

Entry	1	3	4	5	6	8	9	10	11	12
Time (h)	0	3	24	48	72	98	144	192	240	264

IM absorption from Cu(II)-MOF:

Nano $\text{Cu}_3(\text{BTC})_2$ (%) ^a	0.0	7.33	11.05	29.84	43.98	58.54	96.93	- ^b	-	-
Bulk $\text{Cu}_3(\text{BTC})_2$ (%)	0.0	6.78	22.77	47.05	79.04	80.02	81.12	-	-	-
Carbon active (%)	0.0	2.22	4.87	10.10	12.11	15.01	34.03	-	-	-

IM release from Cu(II)-MOF:

Nano $\text{Cu}_3(\text{BTC})_2$ (%)	0.0	14.34	47.55	52.06	52.23	52.50 ^d	52.98	53.54	58.96	59.08
Bulk $\text{Cu}_3(\text{BTC})_2$ (%)	0.0	17.53 ^c	67.72	69.17	70.39	86.36 ^d	88.97	89.02	90.70	-

a) % drug dried material,

b) Not measured,

c) t= 2 h,

d) t= 96 h.

Graphical Abstract:

Controlled uptake and release of imatinib from $\text{Cu}_3(\text{BTC})_2$ metal-organic framework.