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Abstract

The micron and nanometer sized γ-cyclodextrin metal-organic frameworks (γ-CD-MOFs) were successfully synthesized using microwave technique for the first time for rapid and facile synthesis. Polyethylene glycol 20000 (PEG 20000) was used as surfactant to control the size and morphology of γ-CD-MOFs. The as-synthesized γ-CD-MOFs were characterized using various techniques, including X-ray powder diffraction (PXRD), scanning electron microscopy (SEM), thermogravimetric analysis (TGA) and N_2 adsorption. The increment in the reaction time and MeOH ratio dramatically damaged the crystalline integrity of γ-CD-MOFs. Fenbufen was selected as a model drug to evaluate the loading characteristics of γ-CD-MOF crystals. In results, the nanometer sized γ-CD-MOFs (100-300 nm) showed rapid and higher adsorption (196 mg· g^{-1}) of Fenbufen in EtOH when compared with the micron crystals. The adsorption parameters fitted well to a pseudo-second-order kinetic model and chemisorption of Fenbufen was further supported by molecular docking illustrations. In summary, the control synthesis of γ-CD-MOFs was successfully achieved by microwave assisted method and resultant crystals were further evaluated for potential drug delivery applications.

Keywords: Cyclodextrin-metal-organic frameworks; microwave; PEG 20000; drug loading; crystallinity

Title Page

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Introduction

Metal-organic frameworks (MOFs) have emerged as a new class of nanoporous materials with wide range of applications in molecular recognition,[1] gas storage,[2] catalysis[3] and drug delivery.[4] Usually, they are constructed from metal ion connectors and organic bridging ligands.[5] Contrary to conventional porous material,[6, 7] the pore size and inner surface characteristics of MOFs can be modulated by tuning the size and shapes of the linkers.[8]

The sizes and shapes of MOF materials are critical for their various applications. Therefore, much efforts have been directed to shorten the synthesis time and to

produce uniform crystals using microwave-assisted,[6] mechanochemical[7] and sonochemical[8] methods. At the same time, several strategies have been adopted for controlling the size and morphology of MOFs by altering the synthetic parameters including temperature, processing duration, metal source and solvents. For example, Ban et al reported the morphology control synthesis of ZIF-78 materials by adjusting the nutrient and ligand concentrations.[9] Pan et al reported a facile synthesis method using cetyl trimethyl ammonium bromide as a capping agent for controlling the size and morphology of ZIF-8 crystals in aqueous systems.[10] Cheng et al presented a solvothermal method for control synthesis of NH_2-MIL-53 by altering the DMF and water ratio without adding any surfactants or capping agents.[11]

In recent years, there has been a growing interest in encapsulating drugs in MOFs (Table S1). However, it is very necessary to consider the biocompatibility of material compositions for biomedical applications. Thus, appropriate natural molecules such as amino acid,[12] peptides[13] and nucleobases[14] as well as metal ions (Ca, Mg, Zn, Fe) are considered to be biocompatible as organic linkers and metal connectors of MOFs, respectively. In addition, some post-synthetic modifications of MOFs with biofriendly functionalized linkers also showed their advantages over other reactive groups in various structures.[15, 16]

Recently, Stoddart et al reported the synthesis of environmental friendly and renewable cyclodextrin metal-organic frameworks (CD-MOFs) through a vapor-diffusion method.[17] The CD-MOFs are body-centered cubic extended structures prepared from the coordination of γ-CD and potassium ion and possessed large

spherical voids of 17 Å with apertures of 7.8 Å. Among the various MOFs reported so far, CD-MOFs are materials with potential to adsorb gases (N_2, H_2, CO_2 and CH_4) and some other molecules (Rhodamine B and 4-Phenylazophenol) within their pores.[17] Taking advantage of their uniform channels (17 Å) and high local concentrations of OH^- ions, the γ-CD-MOFs were used as template for the synthesis of silver and gold nanoparticles.[18]

The original vapor diffusion method was able to produce cubic crystals (40-500 μm) of γ-CD-MOFs at ambient temperature over the period of a week.[17] A modified method with the addition of CTAB and a controlled incubation time of 26-32 h has been reported to produce γ-CD-MOF crystals, and they succeeded in the preparation of good quality crystals with well-defined shape in the range of several hundred nanometers to millimeters.[19] However, vapor diffusion method is very difficult to fabricate MOFs for mass production and future industrial use. Not long before, a further improved approach for size control of γ-CD-MOFs has also been reported by us with a conventional vapor diffusion technique, which took about 6 hours.[20] In addition, the previous size modulator of CTAB was quite toxic for cells.

In this paper, we report a fast synthesis of γ-CD-MOFs within several minutes under microwave irradiation. More importantly, PEG 20000, a pharmaceutical excipient, was used as the size modulator for the first time herein. In addition, we could efficiently control the size and morphology of the obtained γ-CD-MOF crystals well by optimizing the reaction time, temperature and solvent ratio in the synthesis process. Fenbufen was selected as drug candidate to investigate the drug loading behavior of

the crystals.

Experimental Section

Materials and Physical Measurements

γ-cyclodextrin (γ-CD, MaxDragon biochem Ltd), potassium hydroxide (KOH, 85.0%, Sinopharm Chemical Reagent Co., Ltd), methanol (MeOH, 99.5%, Sinopharm Chemical Reagent Co., Ltd), polyethylene glycol 20000 (PEG 20000, MW ~ 20000, Ourchem, Sinopharm Chemical Reagent Co., Ltd), ethanol (EtOH, 99.7%, Sinopharm Chemical Reagent Co., Ltd) and dichloromethane (DCM, 99.5%, Sinopharm Chemical Reagent Co., Ltd). Fenbufen (FBF, >99.5% purity) was purchased from Dalian Meilun Biotech Co., Ltd (China). Pure water (18.4 MΩ cm) used in all experiments was purified by a Milli-Q system (Millipore, Milford, MA, USA). All other chemicals were of analytical grade and used without further purification.

Synthesis of γ-CD-MOFs

A mother solution (Figure S1) was prepared by mixing γ-CD (324 mg) and KOH (112 mg) in pure water (10 mL) with pre-addition of 6 mL MeOH, which was sealed and placed in a glass vessel. The mixed solution was heated at 40 ~ 100 °C through microwave irradiation (CEM, Discover, USA) with power (100 w) for 1 ~ 120 min and the clear solution was obtained. Then 256 mg of PEG 20000 was added quickly to trigger the rapid deposition of crystalline materials (precipitation). 60 min later, the micron sized MOF crystals were collected after separation, washed with 15 mL EtOH and MeOH twice and dried overnight at 50°C under vacuum. In parallel experiments, the size of the γ-CD-MOF crystals was modulated by altering the different processing

parameters such as, reaction time (t), temperature (T), solvent ratio (R) of water to MeOH (v/v) and modulators (M). The synthesis procedure of nanometer sized crystals was the same as that for micron sized γ-CD-MOFs. During the size modulation process, 16 mL of MeOH with/without 128 mg of PEG 20000 was added to the reaction solution (F14 and F15) and the final solution was then heated at 50 °C for 10 min. The resulting samples were identified as F1 to F15, the conditions employed in the controlled preparation and the morphology results of these samples are summarized in Table 1. In comparison, the preparation of γ-CD-MOFs (identified as F16) by conventional vapor diffusion method was also investigated according to Smaldone's work (Supporting information S1).[17]

Table 1. Summary of synthesis conditions of F1-F15 samples

Samples	Heating time, t (min)	T (°C)	R	M	Incubation time, t (min)	Results (Morphology)
F1	1	50	10: 6	PEG 20000	60	Typical cubes
F2	10	50	10: 6	PEG 20000	60	Typical cubes
F3	20	50	10: 6	PEG 20000	60	Typical cubes
F4	60	50	10: 6	PEG 20000	60	Typical cubes
F5	120	50	10: 6	PEG 20000	60	Typical cubes
F6	10	40	10: 6	PEG 20000	60	Non-typical Cubes
F7	10	60	10: 6	PEG 20000	60	Typical cubes
F8	10	80	10: 6	PEG 20000	60	Typical cubes
F9	10	100	10: 6	PEG 20000	60	Typical cubes
F10	10	50	10: 4	PEG 20000	60	Non-typical hexagonal shapes
F11	10	50	10: 5	PEG 20000	60	Non-typical Cubes
F12	10	50	10: 7	PEG 20000	60	Typical cubes
F13	10	50	10: 8	PEG 20000	60	Typical cubes
F14	10	50	10: 6	MeOH	60	Non-typical Cubes
F15	10	50	10: 6	MeOH + PEG 20000	60	Non-typical Cubes

Characterizations of γ-CD-MOFs

Morphological characterizations of γ-CD-MOF crystals were conducted by the scanning electron microscope (SEM, S3400, Hitachi). The specimens were immobilized on a metal stub with double-sided adhesive tape and coated with a thin gold film, and then observed under definite magnification.

The crystallinity of the samples was characterized by X-ray powder diffraction (PXRD) analysis. Diffraction patterns of the prepared γ-CD-MOF crystals were detected with a Bruker D8 Advance diffractometer (Bruker, Germany) at ambient temperature, with tube voltage of 40 kV, tube current of 40 mA in a stepwise scan mode ($8°\cdot\ min^{-1}$). All the samples were irradiated with monochromatized CuKα radiation and analyzed over a 2θ angle range of 3 - 40°.

Thermogravimetric analysis (TGA) of γ-CD-MOF crystals was performed using a thermal analysis system (NETZSCH 209F3 240-20-382-L, USA) at a heating rate of 10 °C$\cdot\ min^{-1}$ under nitrogen. Samples were weighed (approx. 5 mg) in a hanging aluminum pan and the weight loss percentage of the samples was monitored from 30 to 400 °C.

Nitrogen adsorption-desorption isotherm was measured with a liquid nitrogen bath (-196 °C) using a porosimeter (Micromeritics ASAP 2020, USA). In order to remove the interstitial solvents, the samples were activated by immersing in dichloromethane for three days and dried under vacuum at 50 °C for 12 h. Known amounts of samples (e. g. 150-200 mg) were loaded into the BET (Langmuir) sample tubes and degassed under vacuum (10^{-5} Torr) at 50 °C for 6 h. BET (Langmuir) model was applied to

measure the specific surface areas of the prepared samples.

FT-IR spectra of samples were obtained using an FT-IR spectrometer (Nicolet Continuum XL, Thermo Fisher Scientific). Briefly, the sample and potassium bromide were mixed well with a ratio of 1:10 followed by being compressed into a disk. 32 scans were carried out in wavenumber 400-4000 cm^{-1} at a resolution of 4 cm^{-1}.

Adsorption experiment

In order to investigate the adsorption behavior of γ-CD-MOFs for FBF in EtOH solution, 50 mg of γ-CD-MOFs were added into 25 mL of FBF solution (600 μg· mL^{-1}) at 30 °C temperature. The suspensions were shaken (150 rpm) and incubated for 24 h. The FBF content of the solution was determined followed by a HPLC method. The adsorption capacity (q) of γ-CD-MOFs towards FBF was calculated as follows:

$$q_t = \frac{V(C_0 - C_t)}{W} \quad (1)$$

where q_t (μg· mg^{-1}) is the adsorption capacity at contact time t, V is the volume of FBF solution (mL), C_0 is the initial concentration of FBF (μg· mL^{-1}), C_t is the concentration of FBF at contact time t (μg· mL^{-1}), and W is the weight of CD-MOFs (mg).

Release of FBF from FBF loaded CD-MOFs in EtOH was also performed. And the detailed methods and results were described in Supporting Information (S5 and Figure S7).

HPLC method for determination of FBF

The analysis was carried out with an Agilent C18 column (4.6 mm × 150 mm, 3.6 μm i.d.) using flow rate of 1.0 mL· min^{-1} at a wavelength of 281 nm. The FBF was

detected with the column temperature of 25 °C, the injection volume of 2 μL and the mobile phase composed of 10% acetonitrile in 0.1% formic acid aqueous solution, changing linearly over 10 min to 90% acetonitrile maintained for 3 min, and then decreasing to 10% in 1 min maintained for 6 min.

Molecular docking of FBF and γ-CD-MOFs

The crystal structure of CD-MOFs was extracted from single crystal structure of CD-MOFs in literature.[21] In the docking model, an expanded non-periodic structure was used, in which the K^+ ion that not affecting rigid docking results was deleted and the OH^- ion was replaced by H_2O. The structure of sucralose molecule was built using the Materials Visualizer module in Materials Studio (MS, Accelrys Inc.) 5.0. The Forcite module in MS was employed for minimization and molecular dynamics (MD) simulation. The docking program AutoDock Vina 1.1.2 was used to perform the automated molecular docking calculation.[22] Detailed method was described in S4.

Results and discussion

In this study, γ-CD-MOFs were synthesized by a microwave irradiation method of γ-CD and KOH in a 1: 8 molar ratio under different reaction conditions. Cubic γ-CD-MOF crystals were obtained by raising the reaction temperature and pre-addition of sufficient reaction solvent. To the best of our knowledge, this is the first report on synthesis of γ-CD-MOFs using microwave irradiation method and PEG as an efficient size modulator. The synthesis procedure was thoroughly optimized as explained in following sections.

Effects of reaction parameters on crystal assembling

Initial investigations revealed that reaction time and solvent ratio were critical to the fabrication of γ-CD-MOFs crystals in microwave irradiation method. Different time

parameters from 1 min to 120 min were considered for the optimization of reaction time. The SEM images of the crystals synthesized at different time intervals revealed the uniform cubic morphologies as shown in Figure 1a. The size of γ-CD-MOFs crystals (1-3 μm) just modulated by PEG 20000 were recorded smaller when compared with those obtained with CTAB by vapor diffusion method,[19] which might be due to the higher number of nucleation sites.

The PXRD results in Figure 1b suggested the high crystallinity of the samples synthesized at different time intervals in agreement with the crystals synthesized by conventional method (Figure S2) and the reported literature.[19] However, the dramatic loss in crystallinity was recorded for prolonged reaction time of 120 min in spite of their cubic shapes. The microwave thermal effects are characterized as a local heating state. While the heating time is increased beyond the optimum level, such deterioration in cubic structure of CD-MOFs may be observed to some extent. Similar phenomenon was also found in the synthetic process of some other samples.[23]

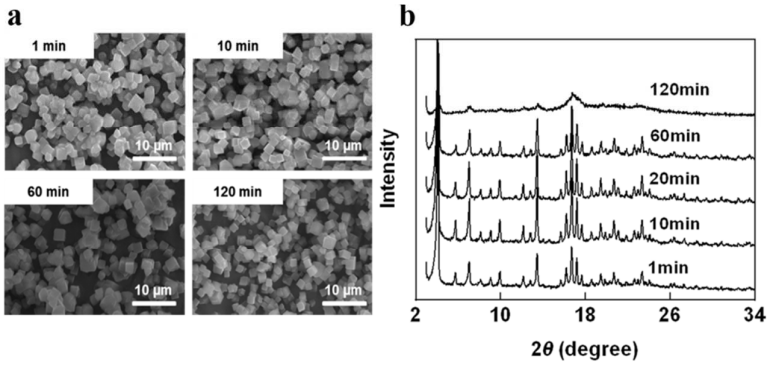

Figure 1. SEM morphology images and PXRD crystallinity patterns of γ-CD-MOF crystals obtained after different time of 1 (F1), 10 (F2), 60 (F4) and 120 (F5) min. The longer reaction time of 120 min showed the destruction of the crystalline structure of γ-CD-MOFs.

In addition to the reaction time, the effect of temperature on the size and morphology of γ-CD-MOFs was also investigated. SEM images of γ-CD-MOF crystals obtained at different reaction temperature of 40, 60, 80 and 100 °C at 10 min were shown in Figure 2a. A significant effect of reaction temperature on the size of γ-CD-MOF crystals was recorded. At lower temperatures, the deposition of white precipitates were observed with the pre-addition of MeOH into the γ-CD/KOH mother solution. The precipitates did not dissolve completely at 40 °C and this observation can be attributed to the rapid over-saturation of the precursors due to pre-addition of excessive MeOH. During the crystallization process, the anti-solvent recrystallization process would be easier and the size of the newly obtained crystals would be functioned by the recrystallization and the size modulator of PEG 20000, finally led to the formation of smaller size of γ-CD-MOF crystals. In order to better control crystals size, the increase of the temperature must be processed. With an further increase of temperature from 50 °C to 100 °C, no distinct influence on the size and morphology of γ-CD-MOFs crystals was observed. The crystalline structure (Figure 2 b) of γ-CD-MOFs does not change with the reaction temperature.

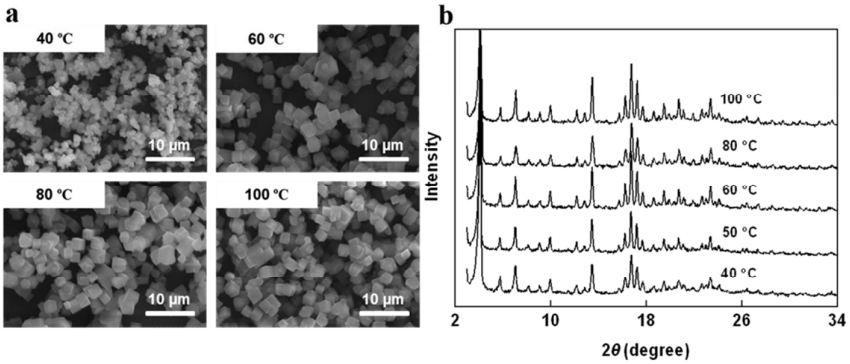

Figure 2. SEM morphology images and PXRD crystallinity patterns of γ-CD-MOF crystals obtained at different temperature of 40 (F6), 60 (F7), 80 (F8) and 100 °C (F9). The increase of temperature from 40 to 100 °C showed no influence on the crystalline structure of γ-CD-MOFs.

γ-CD-MOF crystals with different morphologies were obtained by varying the solvent

ratio (MeOH in MeOH-H_2O) at 10 min and 50 °C. Figure 3a showed the SEM images of the samples synthesized with different water to MeOH ratios. Initially with low MeOH volume, the irregular hexagonal crystals were produced. With increasing the proportion of MeOH to 37.5 vol% at same water content, the uniform cubic crystals were obtained. It was speculated that increment in MeOH volume contributes to the nucleation of MOF crystals due to the thermodynamic stability of crystal face growth. Crystal shape is often a consequence of the coexistence of slower and faster growth facets. With the growth of the crystal, the crystal morphology is dominated by the slower growth facets.[24] Crystalline patterns of γ-CD-MOFs synthesized with different solvent ratios were presented in Figure 3b. It is well-known that the low supersaturation often leads to a decrease in nucleation sites.[25] We expected that less volume of MeOH does not satisfy the level of supersaturation sufficient for the crystals growth. However, it was also observed that excessive volume of MeOH (water: MeOH = 10: 8) would also deteriorate the crystallinity of γ-CD-MOFs.

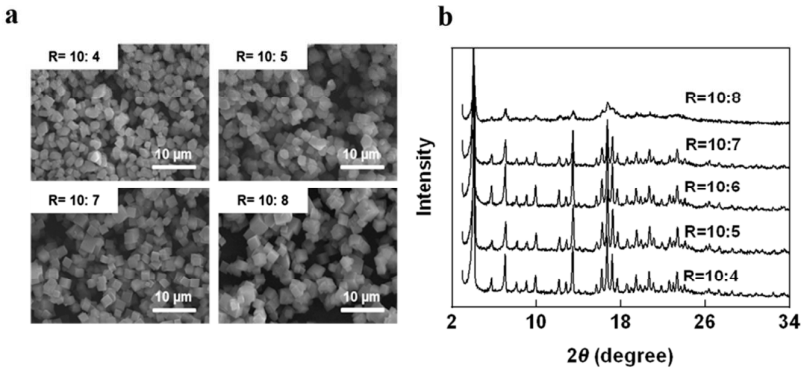

Figure 3. SEM morphology images and PXRD crystallinity patterns of γ-CD-MOF crystals obtained with different ratios of H_2O to MeOH as 10: 4 (F10), 10: 5 (F11), 10: 7 (F12) and 10: 8 (F13). Higher volume ratios of MeOH resulted in γ-CD-MOFs more uniform but caused disturbance of the crystallinity of γ-CD-MOFs.

Size modulator effects

The smaller crystal size in nanometer range could be promising for biological applications and traditional selective separation and catalysis. The crystal size can be adjusted by controlling the nucleation and crystal growth rate.[26] Micron sized γ-CD-MOF crystals can be obtained by simply adding the PEG 20000 as surfactant. MeOH was employed as a size modulator to obtain the nanometer sized crystals. Crystal size of 200-800 nm was recorded by SEM as shown in Figure 4. Furthermore, much smaller crystals of 100-300 nm were obtained by pre-mixing of MeOH with PEG 20000 during modulation process. The crystallinity of nano crystals were found consistent with those of micron sized crystals as shown in Figure 4. Smaller crystals are usually obtained when the nucleation rate is larger than the rate of crystal growth.[27] It could be easily understood that excess volume of MeOH contributed to the oversaturation of the reaction solution, finally resulted in a dramatic decrease of CD-MOF size.

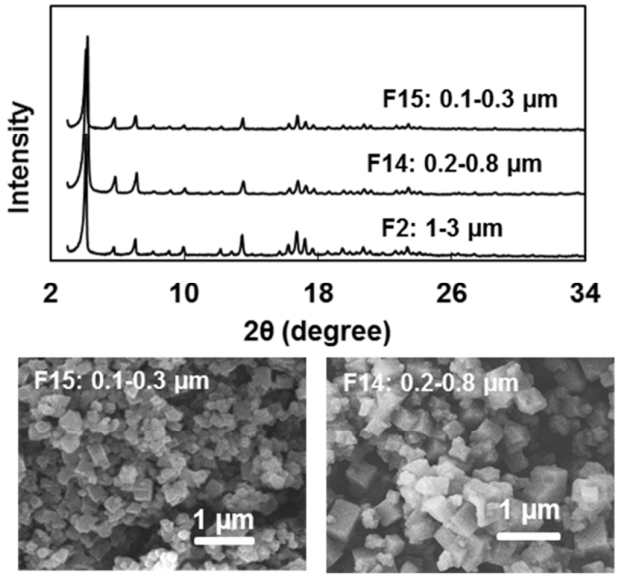

Figure 4. PXRD crystallinity patterns and SEM morphology images of γ-CD-MOF crystals. It shows different sizes of γ-CD-MOFs possess the similar PXRD pattern.

Adsorption isotherms of FBF on γ-CD-MOFs

TGA data (Figure S 4) for DCM treated samples revealed a thermal stability region of crystals following the initial loss due to residual solvent guest molecules. These results directed us to evaluate the porosity of CD-MOF crystals. Not long before, a total of 21 types of model drugs were screened to testify the adsorption capacity of γ-CD-MOFs, wherein, γ-CD-MOFs showed the highest captopril adsorption capability which reached to 19.3% (w/w).[20] Later, sucralose, a kind of non-nutritive sweetener was loaded by γ-CD-MOFs and the thermal stability of this drug was successfully improved, in which the drug loading efficiency for CD-MOF-Micro and CD-MOF-Nano was 17.5 ± 0.9 % and 27.9 ± 1.4% (w/w), respectively.[28]

The N_2 adsorption-desorption isotherms (Figure 5) of activated γ-CD-MOFs of F15 (0.1-0.3 μm), F14 (0.2-0.8 μm), F2 (1-3 μm) and F16 (40-500 μm) (Figure S3) defined a BET (Langmuir) surface area of 673 (751), 1010 (1175), 820 (913) and 1002 (1118) $m^2 \cdot g^{-1}$, respectively. The above BET surface area results clearly illustrated that the surface area of samples of F14 and F16 were larger than others, which obviously indicated that the size modulator of PEG 20000 diminished the BET surface area of γ-CD-MOF crystals. The sample of F15 possessed the lowest BET surface area among these four samples, which could also be due to that some cavities of CD-MOFs being blocked by PEG 20000 molecules. However, the drug adsorption properties of γ-CD-MOFs crystals could not be directly estimated from BET results. Thus, systematic adsorption experiments were set up to optimize their drug adsorption abilities.

Fenbufen, an analgesic and non-steroidal anti-inflammatory drug with a low aqueous solubility and weak acidic nature, was selected for adsorption evaluations. The dimensions of aperture window (7.8 Å) and internal pores (17 Å) are sufficiently large to accommodate the FBF because of its small molecular size. In view of MOFs with different sizes showing different adsorption capabilities towards same small molecular sized compounds[29], the adsorption capability to FBF was investigated using micron and nanometer sized γ-CD-MOFs. The specific sizes and BET (Langmuir) surface area results of used γ-CD-MOFs crystals are detailed in Table 2.

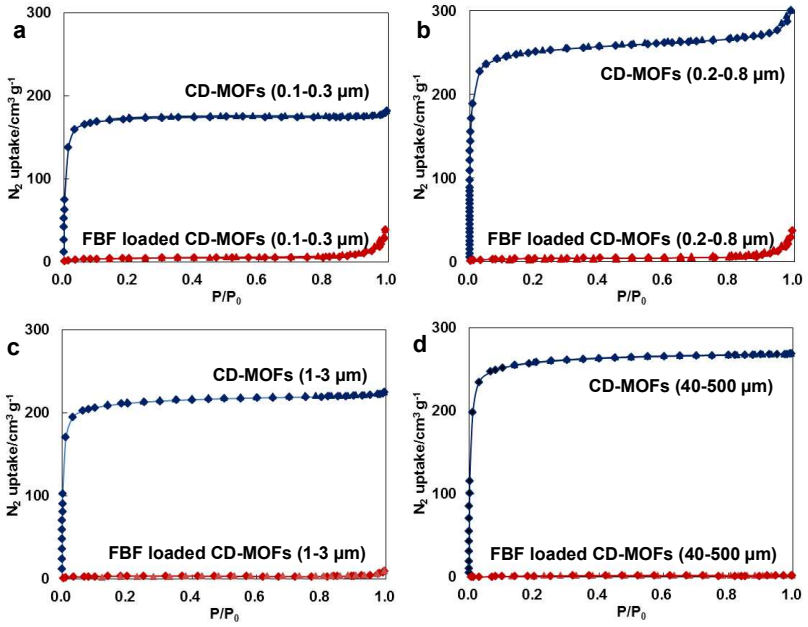

Figure 5. N_2 Adsorption isotherms, for activated and FBF-loaded samples of γ-CD-MOFs of (a) F15 (0.1-0.3 μm), (b) F14 (0.2-0.8 μm), (c) F2 (1-3 μm) and (d) F16 (40-500 μm) measured at 77 K. The N_2 uptake defines a BET (Langmuir) surface area of 673 (751) (F15), 1010 (1175) (F14), 820 (913) (F2) and 1002 (1118) (F16) $m^2 \cdot g^{-1}$.

The effect of FBF incubation time on adsorption capacity is shown in Figure 6a. Gradual increment in adsorption content was noticed with the prolongation of time but varied in micron and nanometer sized γ-CD-MOFs. The crystals of 100-300 nm

(F15) exhibited a rapid and higher adsorption capacity for FBF compared with other γ-CD-MOFs. The F15 sample showed a rapid adsorption during the first 1 h and reached the adsorption equilibrium within 2 h with the highest adsorption capacity of 196 mg· g^{-1} (molar ratio of FBF to CD-MOFs was 1: 1.9). Obviously, the adsorption content of sample F15 in 5 min was similar to that of sample F16 within 24 h.

The obtained data was fitted well to pseudo-second-order kinetic model (see S3 for method details) which suggested the chemisorption behavior of drug adsorption.[30, 31] The coefficients for the linear plots of t/q_t against time for pseudo-second-order kinetics were greater than 0.99 for all systems except F16 ($r^2 = 0.95$, Figure 6b) which might be due to the non-uniformity of F16 crystal sizes. The proposed hypothesis that the FBF molecules occupied most of the crystals cavities was supported by a dramatic decrease in the surface areas of the F2, F14, F15 and F16 crystals (Table 2 and Figure 5). Furthermore, the release rates of FBF loaded γ-CD-MOFs in EtOH were very similar with the adsorption process and the cumulative release percentages of the four samples within 20 h kept 70-85 % (Figure S7).

Table 2. Summary of the size of γ-CD-MOFs (F2, F14, F15, F16)

Samples	Size (μm)	BET (Langmuir) surface area (m^2· g^{-1})
F2	1-3	820 (913)
F14	0.2-0.8	1010 (1175)
F15	0.1-0.3	673 (751)
F16	40-500	1002 (1118)

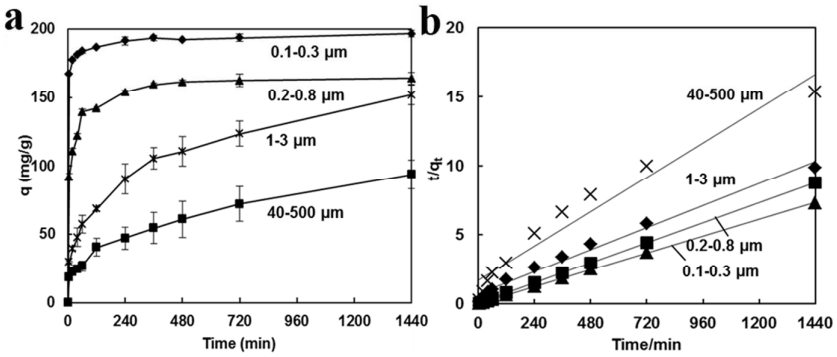

Figure 6. (a) Effects of contacted time on the adsorption of FBF onto Micro and Nanometer sized γ-CD-MOFs (n=2) of F15 (0.1-0.3 μm), F14 (0.2-0.8 μm), F2 (1-3 μm) and F16 (40-500 μm). The crystals with smaller size distinctly show a higher adsorption capacity than larger size CD-MOF crystals. (b) The fitting results of the pseudo-second-order kinetics fit the experimental data well.

FT-IR spectra and molecular docking of FBF and γ-CD-MOFs

The FT-IR spectra of FBF loaded γ-CD-MOFs (F2) samples are shown in Figure 7 in comparison with γ-CD-MOFs and pure FBF. The characteristic C=O stretching vibrations at 1712 cm^{-1} (carboxylic acid) and 1679 cm^{-1} (ketone), the skeletal vibration of phenyl rings at 1600 cm^{-1}, asymmetric and symmetric vibration of carboxylate groups at 1561 and 1402 cm^{-1} were observed for pure FBF. The C=O stretching vibrations at 1712 cm^{-1} disappear/shift after adsorption, providing an indication that FBF molecules are loaded in the cavities of γ-CD-MOFs rather than adsorbed on the surface of the composites.

In order to explain the mechanism of FBF loading by γ-CD-MOFs, computer based molecular docking studies of FBF and γ-CD-MOFs were undertaken. In the case of 1:2 molar ratio for γ-CD and FBF in γ-CD-MOFs, the docking free energy was recorded -7.0 $kcal \cdot mol^{-1}$ and -8.5 $kcal \cdot mol^{-1}$ (Figure S5) for the first and second molecules of FBF, respectively. The simulation results suggested that the two FBF molecules would be favorably positioned in the cavities of D-γ-CDs (dual γ-CD units) of γ-CD-MOFs and the cavity of each γ-CD included one FBF molecule (detailed docking results are described in S4). Figure S6 illustrated that H-bonds can be readily

formed by the carbonyl (-COOH) of FBF with the hydroxyl of D-γ-CDs in γ-CD-MOFs, supported by the shift of C=O stretching vibrations at 1712 cm^{-1} to lower wave number in IR spectra. Considering the carboxyl function group and a small pK_a, the high adsorption capability of γ-CD-MOFs for FBF is believed to arise from the strong electrostatic interaction between the carbonyl group in FBF molecule and potassium ions in γ-CD-MOFs.

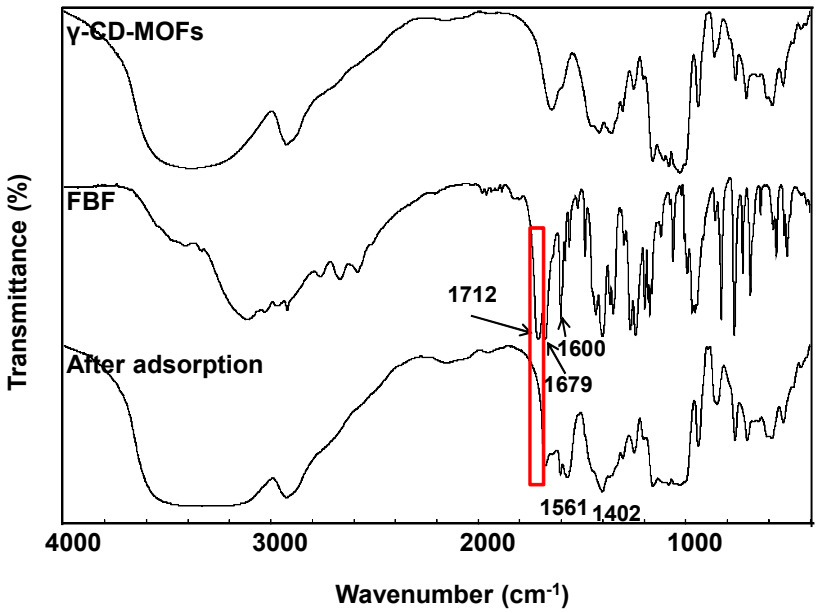

Figure 7. FT-IR spectra of γ-CD-MOFs, FBF and FBF loaded γ-CD-MOFs, respectively.

Conclusions

Microwave method for rapid and controlled synthesis of γ-CD-MOFs was reported. The developed method was able to shorten the hours' long fabrication process into minutes. The size and morphology of γ-CD-MOF crystals have been adjusted by altering the reaction time, temperature and solvent ratio. The PEG 20000 and/or MeOH were successfully employed as size modulators to obtain the nanometer sized crystals. Notably, an increase in the reaction time or MeOH ratio was found to

damage the γ-CD-MOF crystallinity. The nanometer sized γ-CD-MOFs exhibited a faster and higher adsorption capability of 196 mg· g^{-1} for FBF within 24 h compared with the micron sized. Adsorption kinetics of FBF towards γ-CD-MOFs (600 μg· mL^{-1} in EtOH) is described by the pseudo-second-order kinetic model. Molecular docking further illustrated that FBF is likely to be chemisorbed by γ-CD-MOFs. Thus, facile synthesis and size control approaches, together with FBF loading behavior of γ-CD-MOF crystals are providing support for their potential applications in drug delivery.

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Supporting Information

Figure S1 to S7 showing synthesis scheme, SEM, PXRD, molecular docking results and FBF release.

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Manuscript title:

Microwave-assisted rapid synthesis of γ-cyclodextrin metal-organic frameworks for size control and efficient drug loading

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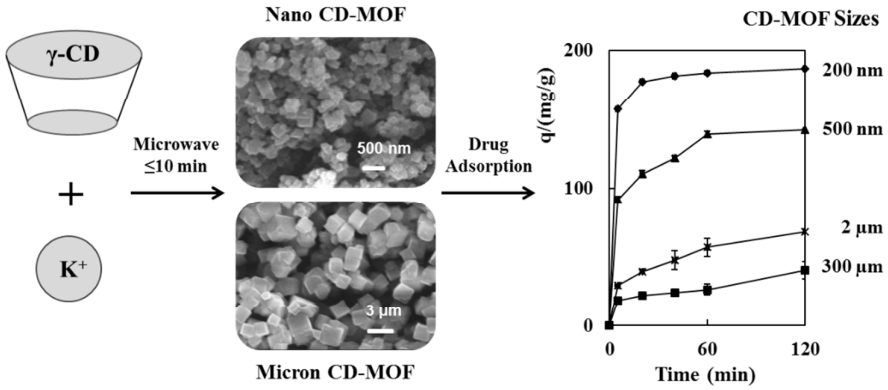

Synopsis:

γ-CD-MOFs were synthesized by microwave-assisted technique for the first time and exploited for drug delivery applications. The size and morphology of γ-CD-MOF crystals can be efficiently controlled by optimizing the synthesis process. Compared with micron crystals, nanometer sized γ-CD-MOFs (100-300 nm) showed rapid and higher adsorption (196 mg· g^{-1}) of Fenbufen which implies the good loading characteristics of γ-CD-MOFs.