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Synthesis of MIL-88(Fe) by "green" method for drug delivery purpose

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ABSTRACT

MIL-88(Fe), a metal-organic framework material has been synthesized by "green" ultrasound method. The MIL-88(Fe) samples were synthesized from a mixture of ferric chloride and 1,4-benzenedicarboxylic acid (H_2BDC) in N,N-dimethylformamide (DMF) at room temperature for 15 mins. The MIL-88(Fe) was characterized by X-ray powder diffraction (XRD) and N_2 adsorption porosimetry(BET). MIL-88(Fe) crystals synthesized under ultrasonic condition produced small and homogeneous crystals. The SEM images of the particles synthesized from this method have approximatedimensions of 200-300nm and hexagonal morphologies. This size reduction is typical of crystals synthesized under ultrasonic condition - a phenomenon which can be attributed to make upuniform and rapid nucleations. The small MIL-88(Fe) crystals are especially effective in the drug delivery fields.

1. Introduction

Metal-organic frameworks (MOFs) are crystalline materials constructed from metal ions or clusters and organic ligands. In recent years, MOFs have attracted considerable attention for their potential applications in many areas such as gas storage, separation, catalysis, optics, photonic, ion exchange, molecular array, biomedicine, sensing and drug delivery [1-8]. The structure and morphology of these materials have to be determined by a proper choice of metals, ligands, and reaction conditions for different purposes.

MIL-88(Fe) (MIL stands for Material of Institute Lavoisier) is the mesoporous iron (III) di-carboxylate MOFs, appears to date as the most promising one, in terms of green synthesis, physicochemical stability, high loading capacities and good degradation/release profile [9-11]. MIL-88(Fe) nanoparticle are built from trimers of iron (III) octahedral connected via ion - ovalent bonds to the terephthalate linker, creating a three-dimensional cubic structure.

In this study, we tried to synthesis MIL-88(Fe) nanoparticle by "green" method for loading 5-fluorouracil as drug delivery system.

2. Experimental

2.1. Material Synthesis

By ultrasound method: MIL-88(Fe) nanoparticles were synthesis at room temperature by an ultrasonic method. 0.270 g $FeCl_3.6H_2O$ is dissolved in distilled water and added 0.166 g terephthalic acid (H_2BDC) in 5 ml DMF for 5 to 15 mins in ultrasonic machine with a frequency of 20 kHz and capacity of 400 W.

By hydrothermal method: Each reaction mixture was prepared by dissolving 0.270 g of $FeCl_3.6H_2O$ and 0.166 g of H_2BDC in 5 mL of DMF. The solution was then transferred to a sealed pressurized PTFE vessel and heated for 2-8 hours at 110°C in an oven.

After the completion of each reaction and before describing characterization, the products were cooled to room temperature before centrifuging, then washed with DMF and dried overnight at 80°C in an oven, yielding the as-synthesized product.

2.2. Characterization

Structure and composition of MIL-100(Fe) nanoparticles were confirmed by different techniques, including

X-ray powder diffraction (XRPD), scanning electron microscope (SEM). The 5-fluorouracil concentration was analyzed by UV-vis spectroscopy from 200 nm to 400 nm with the help of a calibration curve.

2.3. Drug load and release

5-fluorouracil was dissolved in distilled water at a concentration of 20 mg/ml and then added MIL-88(Fe) nanoparticles at a ratio of 1 mg MIL-88(Fe) with 2 ml 5-fluorouracil solution. After that, the mixture was stirred for 24 hours at room temperature. The MIL-88(Fe) with adsorbed 5-fluorouracil was collected by centrifuging (15 min, 6000 round/min) and washing twice with ethanol (1 mL/mg MIL) to remove 5-fluorouracil adsorbed on the outer surface of MIL-88(Fe) and then drying at 80°C for 6 hours in an oven.

The drug-loaded MIL-88(Fe) was dipped in distilling (20 mL/mg MIL@5-FU) for 24 hours at room temperature. The drug release MIL-88(Fe) was gotten out of mixture by centrifuging (15 min, 6000 round/min) and determining the drug concentration. The 5-fluorouracil concentration was analyzed by UV-vis spectroscopy from 200 nm to 400 nm with the help of a calibration curve.

The drug loaded MIL-88(Fe) was placed in a vial and dipped in 5 mL of a dissolution medium (phosphate buffer solution - PBS), pH 7.4 at 37°C. At predetermined time intervals, the dissolution medium was collected by centrifuging and determining the drug concentration. The 5-fluorouracil concentration was analyzed by UV-vis spectroscopy.

3. Results and discussion

3.1. Characterizations of MIL-88(Fe)

X-ray powder diffraction (XRD) of the obtained MIL-88 samples was carried out on the X-ray diffractometer using Cu Kα1 radiation at a scan rate of 5° min^{-1}.

The MIL-88(Fe) was confirmed by comparing the XRD pattern of MIL-88 in this work and the simulated one adopted from literature [12]. The X-ray powder pattern of obtained products show that the products are a crystalline solid, as shown in Fig. 1. The XRD analysis clearly revealed that the obtained products are single phase MIL-88 metal-organic frameworks. The XRD pattern of the as-prepared MIL-88(Fe) is in good agreement with the simulated one, showing the successful fabrication of MIL-88(Fe) material.

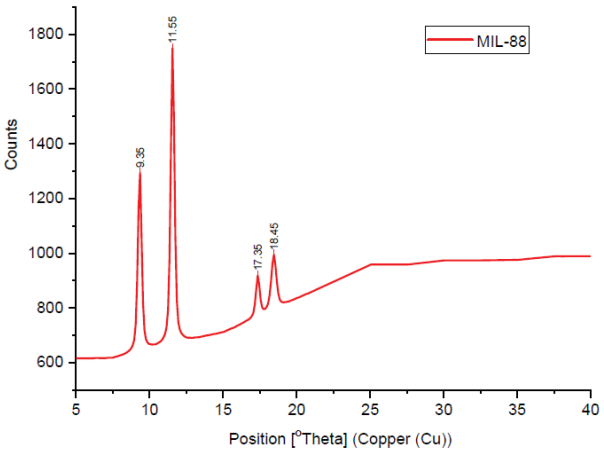

Fig 1. The XRD diagram of MIL-88(Fe) sample.

The morphological details of the product were identified by SEM image is shown in Fig. 2.

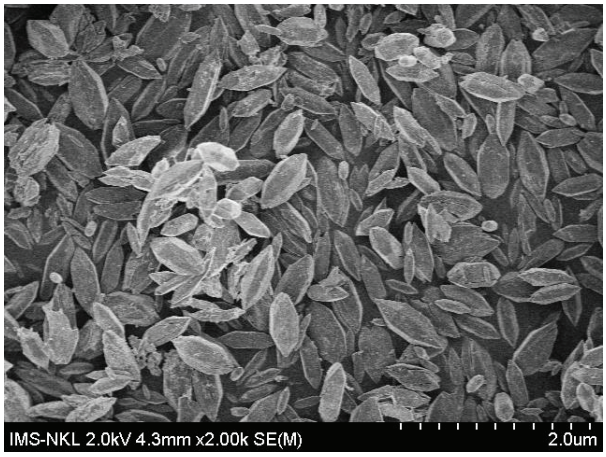

Fig 2. The SEM image of MIL-88(Fe) sample.

The results reveal that the synthesized MIL-88B(Fe) particles exhibit uniform hexagonal micro-rods morphology with an average length of about 500 nm and an average width of 200 nm. Importantly, the particle-size distribution of these MIL-88(Fe) rods are relatively uniform with some exceptions.

The surface area of samples was determined by N_2 adsorption. The Brunauer–Emmett–Teller (BET) analyses were used to assess the storage possibility of molecules in the pores and channels of MIL-88(Fe). BET surface area was measured on a micropore

physisorption analyzer using nitrogen adsorption at 77 K in the range $0.04 \leq P/P_0 \leq 1.00$.

In its dried form, the solids exhibit a negligible adsorption of nitrogen, in agreement with a very narrow pore size. The BET surface area of MIL-88(Fe) sample was 17.4201 $m^2/g \pm 0.0738$. The Barret, Joyner and Halenda (BJH) model were used to the real pore size in the characterization of porous materials. A narrow distribution of pores centered around 9.00 nm the adsorption branch and 8.05 nm the desorption branch of the isotherm, that was suitable for placing drug. The pore diameters of less than 9 nm put the MIL-88(Fe) in microporous materials. In [12], The BET surface area for MIL-88(Fe) is 89 m^2/g in environment treatment purpose.

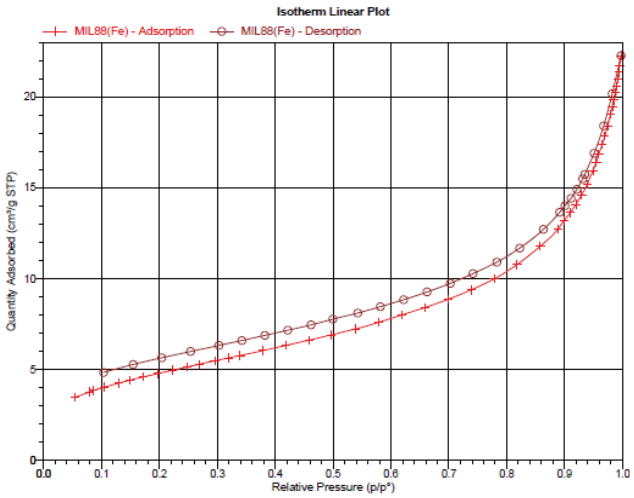

Fig 3. N_2 adsorption-desorption isotherms at 77K of MIL-88(Fe) sample.

The surface area and pore diameter are critical factors for drug adsorption and release in porous frameworks as drug delivery systems. MIL-88(Fe) with wide open channels and the high surface area affording enough space for the passage of small molecules. Pore size determines the size of the molecule that can be loaded in the MIL-88(Fe). Pore diameters slightly larger than the drug molecule dimensions, that allows the loading of the drug into the pores. Therefore, the pore size of the MIL-88(Fe) is suitable for loading 5-FU. According to prolonged - release drug profile, the majority of 5-FU diffused inside the pore and the rest of it adsorbed on the surface of nanostructure MOF.

3.2. The "green" synthesis process

Crystal morphologies of as-synthesized products were examined with SEM. (Fig. 4). Highly crystalline materials were synthesized in 15 minsby an ultrasonic wave. The product yields by an ultrasonic wave were observed less than those obtained bya hydrothermal process. MIL-88(Fe) crystals synthesized under ultrasonic condition produced small and homogeneous crystals, which is a clear indication of efficiency of these two synthesis methods. Despite the different scales which are used to create the SEM images, the particles synthesized from both methods have approximate dimensions of 0.5–1.5 mcm and hexagonal morphologies. This size reduction is typical of crystals synthesized under ultrasonic condition - a phenomenon which can be attributed to make up uniform and rapid nucleations. Furthermore, small MIL-88(Fe) crystals are especially effective in the fields of diffusion, catalysis, and drug adsorption/delivery.

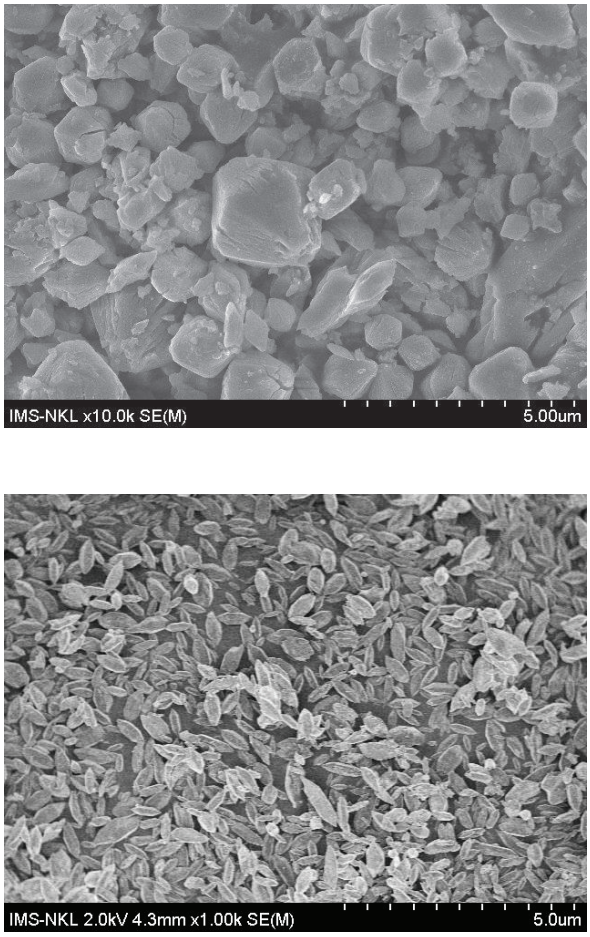

Fig 4. The SEM images of MIL-88(Fe) by hydrothermal process and ultrasound methods.

MIL-88(Fe), a metal-organic framework material has been synthesized by a hydrothermal process , an ultrasonic wave to develop rapidly and energy- efficient alternative synthesis. The operating conditions of each synthesis method was varied to study their effects on product yield and crystallinity.

According to the table 1, the different conditions of each synthesis method were varied their product yield.

Table 1. The product yield for MIL-88Fe synthesized by a hydrothermal process and by an ultrasonic wave.

Method	Time	Yield, %
Hydrothermal process	2 h	1.10
	4 h	6.90
	6 h	24.07
	8 h	58.37
Ultrasound wave	5 min	10.18
	10 min	26.70
	15 min	44.31

3.3. Drug loading - release ability evaluation

Empty MIL-88(Fe) material was soaked in 10 g/l 5-FU solution in 72 hours to examined the ability of loading and releasing drug through morphology, 5-FU concentration after immersing in simulated body fluid.

0.01g ~~of~~ loaded material soaked in 20ml DMF in 48 hours and 5-FU concentration was determined by UV-Vis spectrometry at wavelength λ_{max} = 267nm. The equation of 5-FU calibration curve is defined as y = 0.051x (R^2 = 0.995) where x is the optical absorption Abs. The result indicates that the adsorption capacity of 5-FU for MIL-88(Fe) was 0.28 g/g.

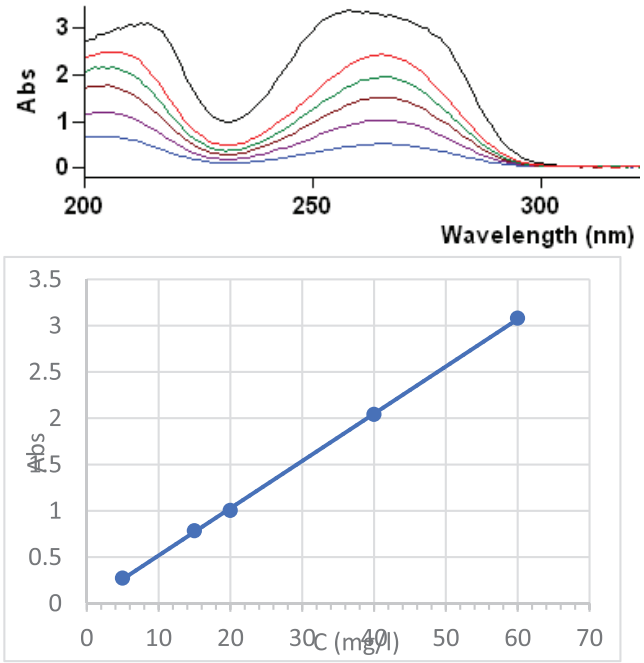

Fig 5. The standard curves of 5-FU concentration.

4. Conclusion

Crystals produced by ultrasonic condition were small and homogeneous, whereas those produced by a hydrothermal process had two more different morphologies and sizes. The observed size reduction of crystals synthesized under ultrasonic condition can be attributed make up uniform and rapid nucleations. The non- uniform size distribution of particles produced bythe hydrothermal process is considered as a result of inherently slow heat transfer method and a poor temperature distribution within the reaction mixture. Ultrasonic wave resulted in much lower yields than the hydrothermal process. For the hydrothermal method, time and temperature were shown to have ~~a~~ significant influence on product crystallinity. However, for the ultrasound method, neither the time nor the power had a significant influence on crystallinity, suggesting that the products reached their maximum crystallinity for this method shortly after nucleation. Furthermore, ultrasonic wave consumed far less energy than hydrothermal process, which confirms that this technology is quicker, more efficient and greener alternatives compare with conventional synthesis methods.

References

1. Shilun Qiu, Guangshan Zhu, Coordination Chemistry Reviews 253 (2009) 2891-2911.
2. Ryan J. Kuppler, Daren J. Timmons, Qian-Rong Fang, Jian-Rong Li, Trevor A. Makal, Mark D. Young, Daqiang Yuan, Dan Zhao, Wenjuan Zhuang, Hong-Cai Zhou, Coordination Chemistry Reviews 253 (2009) 3042-3066.
3. Yuebo Yu, Yuqian Ren, Wei Shen, Huimin Deng, Zhiqiang Gao, Trends in Analytical chemistry 50 (2013) 33-41.
4. Akbar Bagheri, Mohsen Taghizadeh, Mohammad Behbahani, Ali Akbar Asgharinezhad, Mani Salarian, Ali Dehghani, Homeira Ebrahimzadeh, Mostafa M. Amini, Talanta 99 (2012) 132-139.
5. Jesse L.C. Rowsell, Omar M. Yaghi, Microporous and Mesoporous Materials 73 (2004) 3-14.
6. Patricia Horcajada, Tamim Chalati, Christian Serre, Brigitte Gillet, Catherine Sebrie, Tarek Baati, Jarrod F. Eubank, Daniela Heurtaux, Pascal Clayette, Christine Kreuz, Jong-San Chang, Young Kyu Hwang, Veronique Marsaud, Phuong-Nhi Bories, Luc Cynober, Sophie Gil, Gérard Férey, Patrick Couvreur and Ruxandra Gref, Nature Materials, 9 (2010) 172-178.

7. Sarwar Beg, Mahfoozur Rahman, Atul Jain, Sumant Saini, Patrick Midoux, Chantal Pichon, Farhan Jalees Ahmad and Sohail Akhter, Drug Discovery Today 22(4) (2017) 625-637.
8. M. Giménez-Marqués, T. Hidalgo, C. Serre P. Horcajada, Coordination Chemistry Reviews, 307-2 (2016) 342-360.
9. Hee Jung Lee, Yea Jin Cho, Won Cho, and Moonhyun Oh, ACS Nano 7 (1) (2013) 491-499.
10. P. Horcajada, F. Salles, S. Wuttke, T. Devic, D. Heurtaux, G. Maurin, A. Vimont, M. Daturi, O. David, E. Magnier, N. Stock, Y. Filinchuk, D. Popov, C. Riekel, G. Férey and C. Serre, Journal of American Chemistry Society 133 (2011) 17839.
11. C. Gaudin, D. Cunha, E. Ivanoff, P. Horcajada, G. Chevé, A. Yasri, O. Loget, C. Serre, G. Maurin, Microporous and Mesoporous Materials 157 (2012) 124-130.
12. 12. Suzy Surblé, Christian Serre, Caroline Mellot-Draznieks, Franck Millange, Gérard Férey, Supplementary Material (ESI) for Chemical Communications, The Royal Society of Chemistry 2005.