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# Study on "green" synthetic methods using ultrasonic and microwave methods for Fe-BDC as a drug carrier

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**Abstract**

In this study, the metal organic frameworks Fe-BDC were fabricated from ferric salt and 1,4-dicarboxylic acid in DMF by three methods for various time intervals. The prepared materials were characterized by using the scanning electron microscopy (SEM), X-ray diffraction (XRD) and infrared spectroscopy (IR). The loading and release of 5-FU from Fe-BDC was investigated. The 5-FU loading range was more than 520 mg 5-FU/g Fe-BDC and Fe-BDC released over 80 % of the 5-FU for 24 hours.

**Keywords.** Metal-organic frameworks, drug delivery, 5-fluorouracil, green synthesis.

## 1. INTRODUCTION

Metal-organic frameworks (MOFs) have emerged as a novel class of porous coordination polymers. These revolutionary materials have exerted a great influence on a wide range of research fields and industries, including fuel storage, catalysis, energy conversion, gas separation, and biomolecule delivery, due to their structural diversity and large surface area. In the past decade, more than 80,000 MOFs have been reported due to the flexibility of constituent geometry and functionality.[1] MOFs are usually synthesized by solvothermal method that require toxic solvents, involve long process times, and pose health and environmental concerns.[2,3] The most common solvothermal synthesis methods for MOFs involve non-renewable polar solvents, organic compounds, and high boiling conditions. Although the advent of reusable and recyclable solvents is a welcome development, elimination of hazardous organic compounds is preferable. Green synthesis methodologies can employ nontoxic solvents or solvent-free approaches.

The 12 principles of green chemistry can be adapted to synthesis of MOFs.[4] These standards address fundamental procedural aspects that cover utilization of nontoxic solvents and safer reagents, energy efficiency, renewable feedstock, elimination of waste, and biodegradable final products. Green and scalable synthesis of MOFs can be evaluated on the basis of (a) biocompatible building blocks, (b) reduced energy input, (c) safe reaction media (such as water and supercritical solvents), (d) continuous production approaches, and (e) performance design of MOFs through theoretical predictions.[5-7] [5] [6] [7].

Drug delivery is becoming an extremely demanding science. Over the past few decades, drug delivery systems (DDS) have been developed as the most advancing area of science.[8] Moreover, in the recent years, the growth of nanotechnology has introduced new applications to medical sciences, especially in the field of drug delivery.[9] In the past more over 20 years, MOFs have attracted considerable attention for their potential applications in many areas. To achieve these goals, the structure and morphology of these materials have to be determined by proper choice of metal ions, ligands, and reaction conditions.[10-13] One of the major potential applications for MOFs is in drug delivery, considering their host-guest properties and facile modification via chemical synthesis.[14-16] Although a lot of materials have shown suitable drug loading capacity and tunable drug release behavior, the study of drug delivery in MOFs is still scarce. More recently, nano-scale metal-organic frameworks (NMOFs) were utilized for efficient drug loading

and delivery.[17-19]

This study presents green synthetic methods of MOFs based on Fe(III) and benzene-1,4-dicarboxylate and investigates its ability in loading and slow-release 5-fluorouracil.

## 2. EXPERIMENTAL

### 2.1. Materials and method

Ferric chloride hexahydrate ($FeCl_3.6H_2O$), 1,4-benzenedicarboxylic acid or terephthalic acid ($C_6H_4(COOH)_2$), N, N- dimethylformamide (DMF), ethanol ($C_2H_5OH$) and 5-fluorouracil ($C_4H_3FN_2O_2$) were purchased from from Sigma Aldrich.

The synthesized Fe-BDC were characterized using X-ray diffraction (XRD) X'Pert Pro type anode $CuK_\alpha$ radiation in a range $2\theta$ = 5-30$^o$ and Fourier transform infrared (FTIR) Tensor II, KBr pellet, scan range of 400-4000 cm$^{-1}$. Morphology of the materials was observed using scanning electron microscopy (SEM) HITACHI S-4600. Nitrogen sorption isotherm was measured using a static volumetric apparatus micromimetic TriStar II 3020 after the sample activated at 393 K.

### 2.2. Synthesis of Fe-BDC

- *Solvothermal method:* 1,4-benzenedicarboxylic acid ($H_2BDC$) as an organic linker was used to synthesize Fe-BDC by solvothermal method. 1.66 g of $H_2BDC$ and 2.70 g $FeCl_3.6H_2O$ were dissolved in 50 mL of DMF and loaded into a Teflon-lined steel autoclave and heated under autogenous pressure at 130 $^o$C for 8 hours. After that the solution was centrifuged. The material was purified in boiling DMF, washed with ethanol/water mixture (ratio of 1/1) and dried at 80 $^o$C for 4 hours.

- *Ultrasonic method:* Ferric chloride hexahydrate (2.70 g) was dissolved in 10 mL DMF, while $H_2BDC$ (1.66 g) was dissolved in 40 mL DMF. Each solution was stirred separately for 15 min then mixed and sonicated with 30 mins. The produced white precipitate was washed with boiling DMF and ethanol/water mixture (ratio of 1/1), and dried at at 80 $^o$C for 4 hours.

- *Microwave method:* The microwave method was used in the synthesis of Fe-BDC. Ferric chloride hexahydrate (2.70 g) and terephthalic acid (1.66 g) were dissolved in 50 mL DMF. The solution was placed in a microwave oven and irradiated at 800 W for 3 mins. The solid was centrifuged in DMF and ethanol/water mixture (ratio of 1/1). The obtained solid was dried at 80 °C for 4 h.

### 2.3. 5-Fluorouracil loading and release

For drug loading, 10mg of dried Fe-BDC was firstly dispersed in 5 mL phosphate buffer solutions (PBS, pH = 7.4) with assistance of 10-minute sonication; subsequently, 10 mL of 5-FU 10mg/mL solution was added to the Fe-BDC dispersion; the loading process was allowed to run at 25 °C for 72 h. At various time intervals, the unloaded drug amount was determined by UV-Vis spectroscopy. A calibration curve of 5-FU was established through measuring the absorbance of characteristic absorption of 5-FU solution with known concentrations at 265 nm. The content of 5-FU was calculated on the basis of the standard curve of Abs (265) versus the 5-FU concentration. The content of loaded 5-FU ($q_t$) by the Fe-BDC was calculated by equation 1:

$$q_t = \frac{(C_0 - C_t) \times V_0}{m} \quad (1)$$

where $q_t$ is the content of loaded 5-FU onto the unit mass of Fe-BDC (mg. g$^{-1}$); $C_0$ (1 mg. mL$^{-1}$) and $C_t$ are the concentrations of 5-FU in the initial dispersion and in the supernatant at time t, respectively; $V_0$ is the volume of the initial dispersion (10 mL); m is the mass of the Fe-BDC (10 mg) in the initial dispersion.

while C = 18.957.Abs - 0.7132 ($R^2$ = 0.9966)

To determine the release profile, 10 mg 5-fluorouracil-loaded Fe-BDC was mixed with 10 mL simulated body fluid at pH 7.4 (PBS) and 37 °C in an Erlenmeyer flask. At various time intervals, the aliquots were centrifuged in order to ensure no solid was left in suspension and the supernatants were analyzed for 5-fluorouracil with UV-Vis spectroscopy at 265 nm. The released percentages (R, %) and release rate were estimated from the following equations:

$$R = \frac{m_t}{m_0} \times 100 \quad (2)$$

$$v = \frac{(m_{t2} - m_{t1})}{\Delta t} \quad (3)$$

where $m_0$ and $m_t$ are amount of 5-fluorouracil loaded into Fe-BDC and released 5-fluorouracil at a definite time; $m_{t1}$ and $m_{t2}$ are amount of release 5-fluorouracil at time $t_1$ and $t_2$, respectively; $\Delta t = t_2 - t_1$. All of tests were made in triplicate and the results were recorded as an average.

## 3. RESULTS AND DISCUSSION

### 3.1. Material characterizations

The crystalline structure of Fe-BDC was determined by the PXRD pattern. In figure 1, the diffraction peaks are similar to the corresponding simulated pattern, which proves the formation of Fe-BDC via three synthesis methods.[20-22]

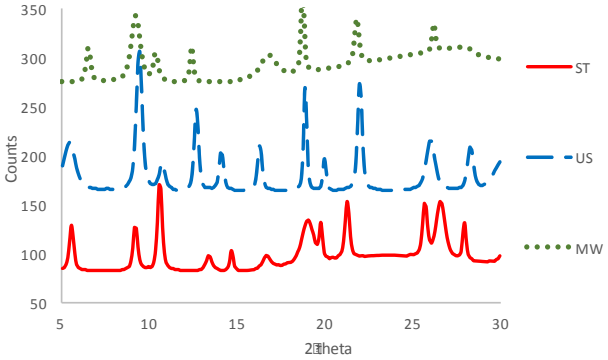



*Figure 1:* The XRD patterns of Fe-BDC

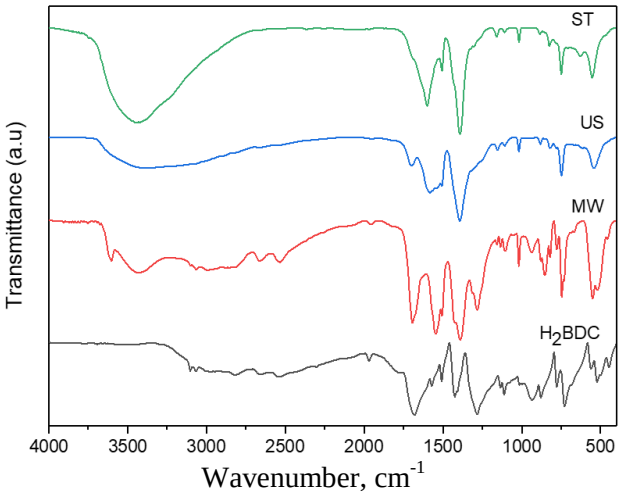
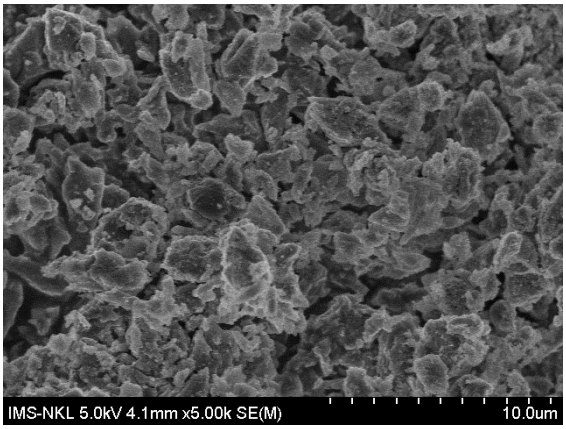
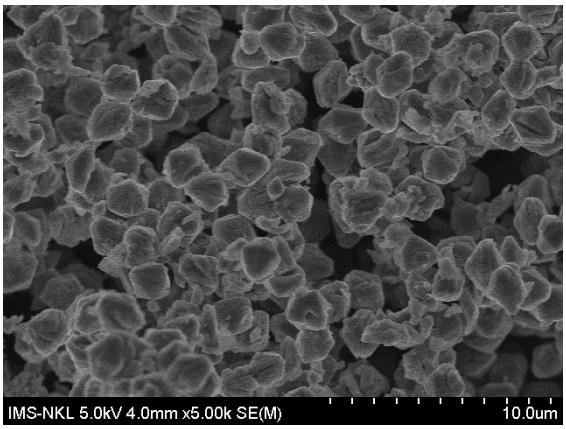



*Figure 2:* The FT-IR spectra of Fe-BDC

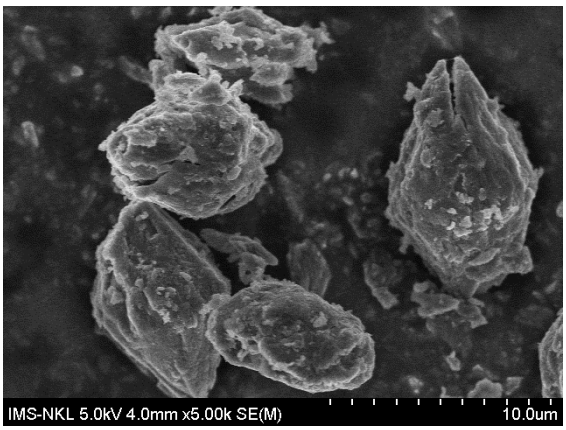
Figure 2 showed the FT-IR spectra of Fe-BDC in the range of 400-4000 $cm^{-1}$. It can be exhibited that a broad peak at ~ 3440 $cm^{-1}$ due to the -OH stretching mode respectively in the FT-IR spectra of Fe-BDC. Another peak related to the presence of adsorbed water was observed at ~ 1600 $cm^{-1}$, assigned to the bending band of the -OH group. Meanwhile, the peak at ~ 1500 $cm^{-1}$ and ~ 1390 $cm^{-1}$ corresponded to the presence of the carboxylate ligand, which was indicative of the coordination of $H_2BDC$ to the iron ion.[23] In this pattern can also be observed the characteristic of aromatic group by the stretching vibration of C=C and -C-C from the aromatic ring (triple peaks at ~ 1160, 1110 and 1020 $cm^{-1}$).[24] The peak at ~ 750 $cm^{-1}$ corresponds to C-H bonding vibrations of the benzene rings. The presence of ν(Fe-O) at ~ 550 $cm^{-1}$, indicating the formation of a metal-oxo bond between the carboxylic group of 1,4-benzene dicarboxylic acid and the Fe(III).[25]




(a)




(b)




(c)

*Figure 3:* The SEM images of Fe-BDC synthesis via solvothermal (a) for 8 hours, ultrasound (b) for 15 mins and microwave (c) for 3 mins

The morphology of synthesized Fe-BDC and its size were studied by SEM. Figure 3 shows typical SEM images of the fully crystallized Fe-BDCs obtained by the three methods. The morphologies, especially those obtained under US condition, are very homogeneous, which shows the purity of the crystallized phase and the efficiency of this synthesis

by the US method. Even though the SEM images of Fe-BDCs obtained by ST and MW are not so homogeneous (probably due to concomitant nucleation and crystal growth under ST and MW), the phase should be Fe-BDC based on the similarity of its XRD pattern with those of the other Fe-BDCs shown in figure 1. The SEM images show that US can produce homogeneous and small crystals of Fe-BDC. Small crystals of porous materials are effective in the fields of adsorption, diffusion, and catalysis.

So far not yet comprehensive study has been made to explain why the synthesis time is drastically decreased under microwave or ultrasound irradiation. Instead, several hypotheses[26-28] have been proposed to explain the fast synthesis observed under MW conditions: 1) An increase in the heating rate of the reaction mixture, 2) more uniform heating of the reaction mixture, 3) a change in association between species within the mixture, 4) superheating of the mixture, 5) the creation of hot spots, and 6) enhancement of the dissolution of the precursor gel. According to Conner and co-workers, rapid heating and the creation of hot spots are important factors associated with an increase in synthesis rates under MW conditions.[26,28]

*Table 1:* Comparison among different synthesis methods, power energy and their effects on particle size, yield and morphology

| Method | Reaction time, mins | Yield, % | Power, W/Power energy, kWh | Particle size, µm | Morphology |
|---|---|---|---|---|---|
| ST | 480 | 52.32 | 900<br>7.2 | 1.2-2.4 | Octahedral |
| US | 20 | 75.96 | 1800<br>0.6 | 1.8-2.0 | Octahedral |
| MW | 6 | 79.22 | 800<br>0.08 | 6.0-8.0 | Octahedral |

Ultrasonic method takes advantage of the ultrasound power. In comparison with the conventional energy sources (e.g. electrical heating), ultrasound has been proven superior in terms of simplicity, reduced reaction times and energy efficiency.

### 3.2. 5-Fluorouracil loading and release

*3.2.1. Loading capacity*

The influence of the loading time on the loading capacities of Fe-BDC is critical to identify the equilibrium time at which the material attained its saturation loading point. The influence of loading time was addressed at fixed conditions of 10 mg as carriers' dose (Fe-BDC), pH 6, 25 °C as temperature, 10 mL 5FU as volume and 1 mg/mL as 5-FU concentrations.

*Table 2:* The concentrations of 5-FU in supernatant and the content of loaded 5-FU onto the unit mass of Fe-BDC at various time intervals

| t, hours | $C_t$, mg/mL | $q_t$, mg/g |
|---|---|---|
| 0 | 1.000 | 0 |
| 8 | 0.9331 | 96.9 |
| 16 | 0.8088 | 191.2 |
| 24 | 0.7215 | 278.5 |
| 48 | 0.5143 | 485.7 |
| 72 | 0.4733 | 526.7 |
| 96 | 0.4762 | 523.8 |
| 120 | 0.4915 | 508.5 |

For the studied Fe-BDC, it exhibited gradual increment in the loading capacity of 5FU with the loading time intervals until attending their saturation time. The observed saturation times for Fe-BDC are 72 h. The obtained loading quantities of 5FU as this saturation point are 526.7 mg/g. When increasing the loading time, loading quantity of 5-FU into Fe-BDC decreased slight.

*3.2.2. In-vitro release of 5-fluorouracil*

The release of 5FU drug was studied using PBS solution (pH 7.4) at 37 $^{o}$C. The sample exhibits fast and sudden release and more than 50 % of the loaded drug was diffused in the solution after 8 h; and achieve release of over 80 % loaded drug after 24 h (table 2). This was explained to be expected behavior for the weak hydrogen bonds between the adsorbed drug molecules and the external surface of Fe-BDC particles which assist the rapid dissolution and diffusion of 5-FU into the buffer solution. The following stages were suggested for the release of drug from Fe-BDC particles; 1) penetration of the solution within the basal space of the Fe-BDC particles, 2) dissolving of the 5-FU molecules, and 3) diffusion of the dissolved drug molecules into the media. The previous results demonstrate that the synthetic metal-organic framework base on iron particle is promising carriers for 5FU drug in the oral formulation as it of controlled release properties.

*Table 2:* The released percentages of 5-fluorouracil from Fe-BDC

| time, mins | $m_t$, mg | R, % | v, mg.min$^{-1}$ |
|---|---|---|---|
| 10 | 0.051 | 1.48 | $5.1\times10^{-3}$ |
| 30 | 0.330 | 9.57 | $1.4\times10^{-2}$ |
| 60 | 0.553 | 16.03 | $7.4\times10^{-3}$ |
| 90 | 0.778 | 22.55 | $7.2\times10^{-3}$ |
| 480 | 1.952 | 56.58 | $3.04\times10^{-3}$ |
| 1440 | 2.778 | 80.52 | $8.6\times10^{-4}$ |
| 4320 | 2.781 | 80.61 | $1.0\times10^{-6}$ |

## 4. CONCLUSION

Fe-BDCs were fabricated as a carrier for 5-fluorouracil drug by "green" synthesis methods. The synthetic particles appeared as octahedral. The product exhibits very high encapsulation capacity for 5-fluorouracil that reaches more 520 mg/g. Moreover, it exhibits a controlled releasing profile that continued for 24 h at pH 7.4 conditions for oral drug carriers. Finally, the product if of non-toxicity properties and can be applied as a promising carrier for 5-fluorouracil of effective anticancer properties.

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