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Study evaluating the ability of Fe-BDC-PEG to carry and release active ingredient 5-fluorouracil

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***Keywords*— Metal-organic framework, 5 Fluorouracil, drug carrier, ultrasonic method.**

***Abstract*—** *This paper presents the results of 5 fluorouracil carrying-release of iron (III) framework materials with two ligands of 1,4-benzene dicarboxylic acid and polyethylene glycol diacid synthesized by ultrasonic bath method at room temperature. Materials were characterized, and their properties by scanning electron microscopy (SEM) and infrared spectroscopy (FT-IR) techniques showed that the active ingredient was fully adsorbed into the structural framework of the material without changing the shape and size of the material. The evaluation results for the 5-fluorouracil carrying capacity of Fe-BDC-PEG two-ligand Fe-BDC-PEG framework material showed that the drug absorption capacity reached 358.707 mg/g. The slow-release characteristics of the material were also evaluated, indicating that the effective release of the active ingredient came to 94.42% after 7 days, and the maximum after 10 days reached 97.68%. The Fe-BDC-PEG@5-FU drug carrier material system is studied to orient the application of cancer treatment when minimizing side effects based on the slow release of the system.*

I. INTRODUCTION

Metal-organic framework materials (MOFs) are the self-assembly of metal ions as coordination centre and organic ligands as bridges between metal centre [1]. Currently, MOFs have been attracting attention because of their potential applications. In particular, iron(III)-organic framework materials, with advantages such as pore size and large surface area, low toxicity... [2], have been applied in many fields such as catalysis, 3], adsorption [4], sensing [5] and biomedicine [6]. Many methods have been used to synthesize iron(III)-organic framework materials such as hydrothermal, microwave, ultrasonic [6-8] …

5-fluorouracil is a widely used antineoplastic drug treating many malignancies [9]. The mechanism of action of this drug is based on the irreversible inhibition of the enzyme thymidylate synthase and, at the same time, induces incorrect synthesis in cancer cells belonging to the group of anti-metabolites. However, it has the disadvantage of a short half-life and low stability in the biological environment [10], which requires an efficient drug delivery-carrying system to overcome. One of the potential applications of iron(III)-organic framework materials is in drug conduction-carrying-drug delivery due to their biocompatibility and ability to absorb large amounts of drugs. Its capability has been demonstrated with many drugs such as busulfan, doxorubicin, ibuprofen, aspirin, etc. [11-14]

This paper presents research results on the 5-fluorouracil carrying and releasing capacity of iron(III)-organic framework materials with a mixture of 2 ligands, 1,4-benzene dicarboxylic acid (H_2BDC) and polyethylene glycol di-acid synthesized by ultrasonic technique at room temperature, orienting its application in cancer treatment.

II. EXPERIMENTS

- Chemicals: Polyethylene glycol 250 di-acid, 1,4-benzene dicarboxylic, iron (III) chloride, dimethyl-formamide,

ethanol, 5-fluorouracil, phosphate buffered saline, all according to Sigma-Aldrich USP standards.

- Tools and equipment: Ultrasonic tank; Ketong-101 heating cabinet; Hittech high-speed centrifuge (Netherlands); Philip dry air dryer (Taiwan).

- Synthesis of Fe-BDC-PEG materials: Dissolve 1.35 g $FeCl_3.6H_2O$ (5.10^{-3} mol) in 25 ml of DMF in a 200-ml plastic beaker, and stir well; Add 0.42 g of H_2BDC dissolved in 100 ml of DMF, and add 0.5 ml of polyethylene glycol 250 di-acid. Transfer the entire solution to a plastic beaker containing FeCl3, and react in an ultrasonic bath for 2 hours; Centrifuge to remove the solids in the mixture after the reaction. Wash the product with DMF solvent at 50°C after 30 minutes of soaking. Rinse with a water/ethanol mixture solvent (1:1 ratio). Dry the product at 80°C for 6 hours.

- Characterization of materials: Determination of functional groups and material formation through FT-IR infrared spectroscopy on Bruker instrument. Morphology and size of materials through scanning electron microscopy (SEM) imaging. Material surface parameters by N_2 isothermal adsorption method (BET) on TriStar II Plus 2.03 physical adsorption device.

Determination of drug-carrying capacity of the material: 0.01g empty Fe-BDC-PEG was soaked in 10 ml of 5-FU 1 g/l active ingredient solution for 72 hours. A centrifuge separates the material from the solution and determines the concentration of the 5-FU solution after the material has been removed the drug from the solution. On the other hand, soak the material after loading the drug in 10 ml of PBS solution at 37 °C after different times, filter and separate the material and determine the concentration of 5-FU. Measure UV-Vis spectrophotometer for PBS solution immersed in drug carrier at λ_{max} = 265 nm on the Drawell DV-8200 device. The 5-FU standard curve equation built through the dependence of light absorbance on the concentration of the solution at wavelength λ = 265 nm is C = 4.69*Abs + 1.003 (R^2 = 0.9918).

III. RESULT AND DISCUSSION

3.1. Characterization

The morphology of the materials before and after the 5-fluorouracil application, as observed through scanning electron microscopy (SEM) images, is shown in Figure 1 below, indicating that the material before and after the 5-FU application has a small size. The size and morphology are almost unchanged, and the morphology is in the form of long grains with a length between 100-120 nm and a grain diameter of about 15-20 nm. The difference observed through SEM images is that the drug-loaded material tends to cluster together. That may be because, in addition to the bonding force between the crystals of the material, there is also the formation of bonds between the drug molecules and the crystals of the frame material.

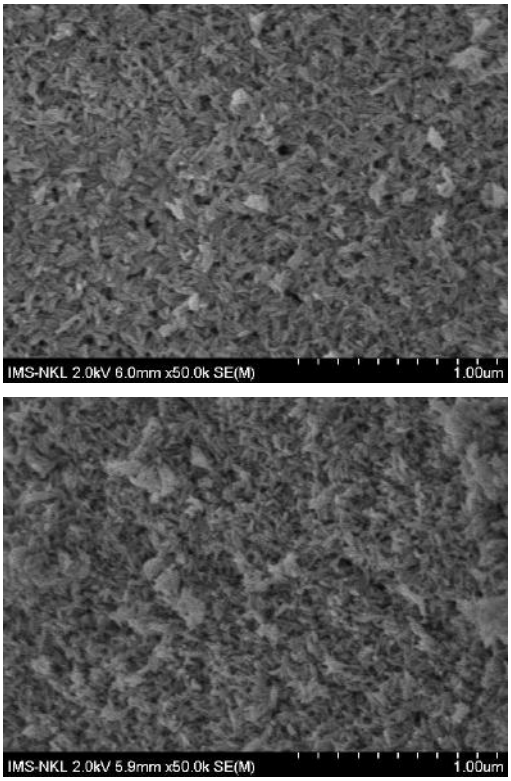

Fig 1. SEM images of Fe-BDC-PEG samples before (left) and after (right) when carrying 5-fluorouracil at 10,000x magnification.

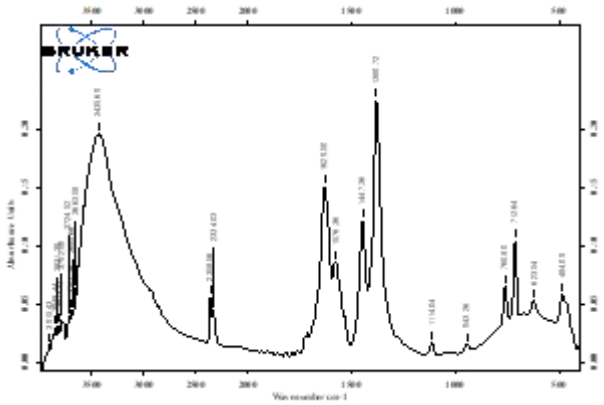

Fig. 2. FT-IR spectra of Fe-BDC-PEG material samples after carrying (adsorption) 5-fluorouracil.

Figure 2 showed the FT-IR spectra of 5-fluorouracil loaded Fe-BDC-PEG in the range of 400-4000 cm^{-1}. The

IR spectrum almost did not show the presence of the 5-FU molecule in the drug-loaded Fe-BDC-PEG except peak at 2358.56 cm^{-1}. However, some small shifts of the peaks can be related to the interaction between Fe-BDC-PEG and 5-FU without participating in forming the bond, only shifting the vibration of the bond. This can be predicted that 5-FU has entered the material's pores; the rest is attached to the surface in small amounts, so there is not enough strength to detect the vibration of the bonds.

The surface characteristics of the materials were evaluated through the N_2 adsorption isotherm method, resulting in the surface area, volume, and pore diameter being 108.967 m^2/g; 0.192 cm^3/g; 7,069 nm, respectively. With this characteristic, the material is promising for carrying high-capacity organic substances.

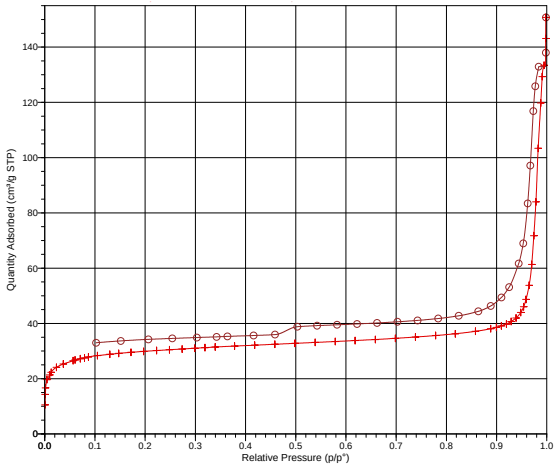

Fig. 3. N_2 isotherm adsorption curve of Fe-BDC-PEG materials.

3.2. The carrying capacity of 5-fluorouracil

The ability to carry the active ingredient 5-FU was assessed through the maximum adsorption capacity after the drug loading process of 72 hours by the UV-Vis photometric method.

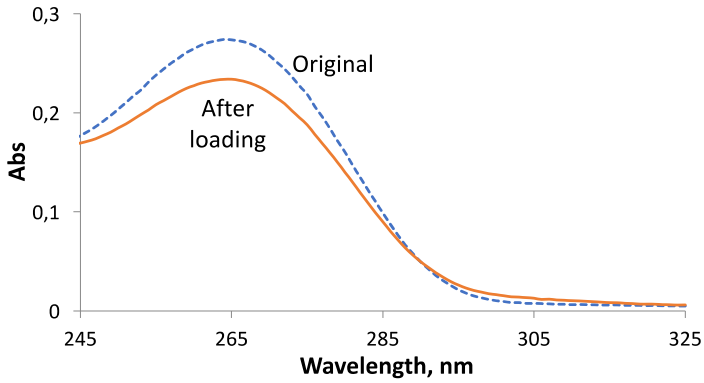

Fig. 4. UV-Vis spectrum of 5-FU solution after drug loading and soaking Fe-BDC-PEG material.

Table 1. UV-Vis photometric results of 5-FU solution after drug loading and soaking Fe-BDC-PEG materials.

	Original solution	Soaking solution
C (dilute 30 times), mg/l	32.599	14.686
C, mg/l	977.984	619.278
q, mg/g	-	358.707

The results of determining the concentration of 5-FU in the dipping solvent of the drug carrier material gave a value of 11.407 mg/l, corresponding to the maximum drug loading capacity of the Fe-BDC-PEG material:

$$Q_{max} = C*V/m_{Fe\text{-}DBC\text{-}PEG} = 358.707\ mg/g.$$

Which in:

- C is the difference in concentration of -FU solution before and after adsorption with Fe-BDC-PEG material, the value determined from the UV-Vis photometric analysis method.

- V is the volume of 5-FU solution used to soak the material: 10 ml ~ 0.01 litter.

- $m_{Fe\text{-}BDC\text{-}PEG}$ is the mass of material used for 5-FU adsorption: 0.01 g.

The results obtained from the determination of the concentration of 5-FU after filtration and separation of materials are much different from the results of soaking, possibly because the concentration of the initial solution is relatively high (1 g/l), so when mixed Dilution with a high coefficient (30 times) for analysis will have a particular error. The solution obtained after letting the adsorbent material shows that Fe-BDC-PEG material can carry the 5-fluorouracil load with relatively high capacity, quite similar to similar material lines like MIL-53(Fe), MIL-88(Fe), MIL-100(Fe) are all capable of carrying 5-fluorouracil with capacities from 160 to 300 mg/g [15]. The results showed that the MIL-53 (Fe), MIL-88 (Fe), and MIL-100 (Fe) are capable of carrying 5-FU with a capacity exceeding 0.131 g/g, 0.28 g/g, and 0.66 g/g.

3.3. Ability to release 5-fluorouracil

Fe-BDC-PEG@5-FU carrier material was immersed in PBS living body simulation solution for different periods at the rate of 0.01g of material in 10 ml of PBS solution. The concentration of 5-FU in the ten times diluted solution was determined by UV-Vis photometric method, giving the results in Table 2 below:

Table 2. *5-FU concentration in PBS solution after different soaking times.*

TT	t, hours	C_t, mg/l	Q, mg/g	Release performance, %
1	1	113.442	113.442	31.63
2	4	114.286	114.286	31.86
3	8	143.035	143.035	39.88
4	12	158.935	158.935	44.31
5	18	168.150	168.150	46.88
6	24	186.150	186.150	51.95
7	72	238.852	238.852	66.59
8	120	291.755	291.755	81.34
9	168	338.702	338.702	94.42
10	240	350.380	350.380	97.68

The survey results on Fe-BDC-PEG's ability to carry and release drugs show that the material can hold and release drugs in a simulated living environment. The active ingredient was removed from the material structure frame after 1 hour, achieved a release efficiency of 31.63%, then continued to release slowly. The drug release rate was relatively fast in the early days, and the drug release efficiency reached 94.42% of the carrier capacity after seven days. However, the drug release rate decreased significantly in the last few days, and the drug release efficiency was 97.68% after ten days. At this time, the amount of medicine left in the material frame is almost gone.

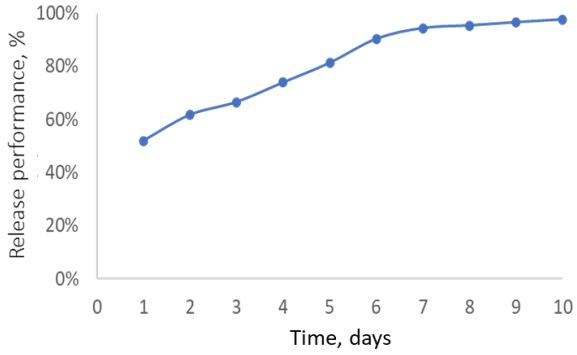

Fig.5. Slow release capacity of 5-FU over time of Fe-BDC-PEG@5-FU carrier material system.

IV. CONCLUSION

Fe-BDC-PEG materials synthesized by ultrasonic method at room temperature have a grain-like morphology with a grain size of about 15-20 nm in diameter and 100-150 nm in length. The material can carry the active ingredient 5-fluorouracil with a carrying capacity of 358.707 mg/g. The effective release of active ingredients reached 94.42% after 7 days, and the maximum after 10 days reached 97.68%. With these results, the Fe-BDC-PEG material is one of the optimal choices for use as a drug carrier for the active ingredient 5-fluorouracil in cancer treatment. The technique of material synthesis and the simple impregnating process of carrying active ingredients from cheap precursors is one of the advantages of choosing this family of compounds for application in therapeutic pharmaceuticals.

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