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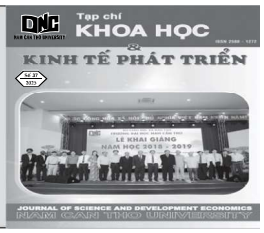

Biocompatible thin films based on ZIF-8 and applying for Tetracycline delivery

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ABSTRACT

New classes of thin films: ZIF-8, mesoZIF-8 and TiO_2@ZIF-8 grated on biocompatible polymers including chitosan (CS) and polyetilene glycol (PEG) were fabricated. The films were carried out in green conditions to apply for drug delivery study. The combination of two polymers PEG and CS enhanced the bonding with the ZIF-8 framework since many function groups have formed in a slightly acidic solution. The resulting of materials were characterized by X-ray diffraction (XRD), scanning electron microscopy (SEM), which revealed the ZIF-cooporated on the polymers well. For the first time, the examination of tetracycline (TC) delivery was studied on these hybrid thin films. The TC delivery was showed in high effective by using the film compared to several materials.

1. INTRODUCTION

ZIF-8, a super member of metal organic frameworks, has been used as a potential carrier in drug delivery due to its hybrid structure of metal and organic ligand, which can enhance strong electrostatic interaction, hydro or π-π bonding with functional group of drugs. In addition, drugs can diffuse into pores because of the flexible structure of the ZIF-8 (Ge, 2022). Sun et al. (2012) early investigated valuable MOFs, and showed a high capacity for drug delivery. In this work, 5-fluorouracil (5-FU) was loaded to ZIF-8 up to 660 mg of 5-FU/g and fast released at a few hours, then slowly after one week. Valuably, the effect of pH value on release speed was examined and gave an important result in using ZIF-8 for drug delivery vehicles. In the following, some medicines loaded to ZIF-8 based on a variety mechanism as told above: 6-mercaptopurine, doxorubicin, celecoxib, or minocycline (Vasconcelos, 2012; Wu, 2015; Wang, 2020).

The preparation of ZIF-8 has been successful through many different routes: traditional solvothermal, microwave, mechanical, or micromixer synthesis. In these studies, dimethylformamide (DMF) appeared as the most common solvent used to produce ZIF-8 because they exhibit a moderate primary condition that

provides further advantages for easy solvent exchange or activation (Lee, 2013; 2015; Li, 2016; Kaur, 2017). However, the utilization of organic solvents causes substantial harm to the environment and increases operating costs. Therefore, focusing on green synthetic routes utilizing less harmful or no organic solvents is the tendency for biological application.

There have been previous studies using water as the solvent for the successful synthesis of ZIF-8, which was described by Pan et al. (2011) for the first time using a high ratio of 2-methylimidazole (Hmim): zinc (70:1) and stirring for 5 minutes at room temperature. The yield approached 80%. Meanwhile, a similar study by Kida et al. (2013) using more dilute conditions at a ratio of Hmim:Zn:water = 60:1:2228 showed truncated rhombic dodecahedron structure of ZIF-8 with high surface areas (1600 m^2/g) and microporous volumes (0.64 cm^3/g). ZIF-8 powder was synthesized by Tanaka (2013) with a Hmim to zinc ion ratio of 1:2, which is 35 times lower than previously seen (about 70:1 in ref), and used non-toxic solvent water with the addition of Pluronic® P-123 surfactant and ammonium hydroxide. Moreover, the synthesis of ZIF-8 under surfactant adding has been known as a green method that can improve the pore holes and internal specific areas (Zhong, 2022). On the other hand, this material can promote loading of large molecules of dyes or drugs inside the ZIF-8 structure (Sheng, 2012).

Tetracycline (TC) is commonly used for antibiotic adsorption studies on ZIF-8. This adsorbent played a pollutant role in drug delivery in these works. To enhance adsorption amount, ZIF-8 was usually modified by some agents such as copper, iron ion, chitosan grafting to its structure or supported by some orientation template like poly (diallyldimethylammonium chloride) or sodium dodecyl sulfonate to create mesoporous and macro-porous (Mazloom-Jalali, 2020; Saghir, 2021). Hydro bonding and π-π attraction are the major mechanisms of these adsorptions' procedures.

This work aims at the green fabrication thin films based on ZIF-8, which is less energy-intensive and more pH neutral in the procedures. The hybrid ZIF-8 including mesoporous and cooperation with nanoparticle TiO_2 to form core-shell TiO_2@ZIF-8, help enhance the drug loading (Luan Tran, 2019). Finally, these green materials are tested for drug delivery to examine the role of mesoporous and mechanism of delivery. The results and comparison to relevant literature are detailed in the following sections.

2. RESEARCH METHODS

2.1 Synthesis of thin films of TiO_2@ZIF-8

Zinc nitrate hexahydrate ($Zn(NO_3)_2 \cdot 6H_2O$, purity 99%, Sigma-Aldrich), 2-methylimidazole (Hmim, $C_4H_6N_2$, purity 99%, Acros, and ammonium hydroxide (28–30% aqueous solution, Avantor) were used as precursors. Titan dioxit (TiO_2 nanoparticles, purity 98%, Sigma-Aldrid). Tetracycline powder, purity 98%, Sigma-Aldrich). Some natural organic chemicals were supplied by official company in Vietnam. The synthesis of these crystals is following to previous working.

For typical thin films preparation, 10 g the mixture of Chitosan (65%), polypropylene glycol (35%) and Glycerol (5%) was completely dissolved in 40 mL acetic acid solution 5% under stirring at room temperature for 4 h. Then, 1 g each of ZIF-8, its modified crystals and 0.01 g of TC were added to the solution, treated in

ultrasonic bath for 30 min then mixed together. The adsorption time was stirred for 24 hours stirring of 400 rpm at room temperature. The solution was poured to the petri plate about in depth of 1 mm and heated at 60°C overnight.

2.2 Characterizations

X-ray powder diffraction (XRD) patterns were recorded using a Cu Kα radiation (40 mA and 40 kV) source on a D8 Advance Bruker powder diffractometer at a scan rate of 2°/min with a step size of 0.03°. Scanning electron microscopy (SEM) studies were conducted on a JEOL JSM-7600F operated at 10kV.

2.3 Drug release study

The drug release was taken place under pH of 7.4 level solution. In this part, 10 mg of thin film of ZIF-8@TC was separately added to 20 mL of each buffer. Then, the solution was stirred at room temperature for 2 days. At each time (1, 4, 8, 12, 24, and 48 h), 2 mL of the solution was taken out and then was quickly replaced with the same amount of fresh buffer. The amount of drug release from samples was recorded by a UV-Vis spectrometer as above describe. Finally, the release percentage (H%) was calculated by the equation:

$$H(\%) = \frac{m_t}{m_o} \times 100$$

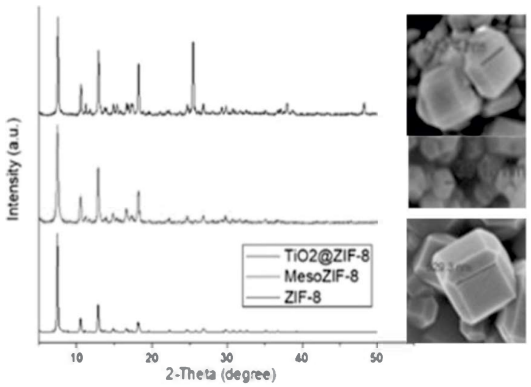
Where:

-m_t: Drug in the film at the time t (mg)

-m_o: Initial loaded drug in film (mg)

3. RESULTS AND DISCUSSION

3.1 Characterization of materials

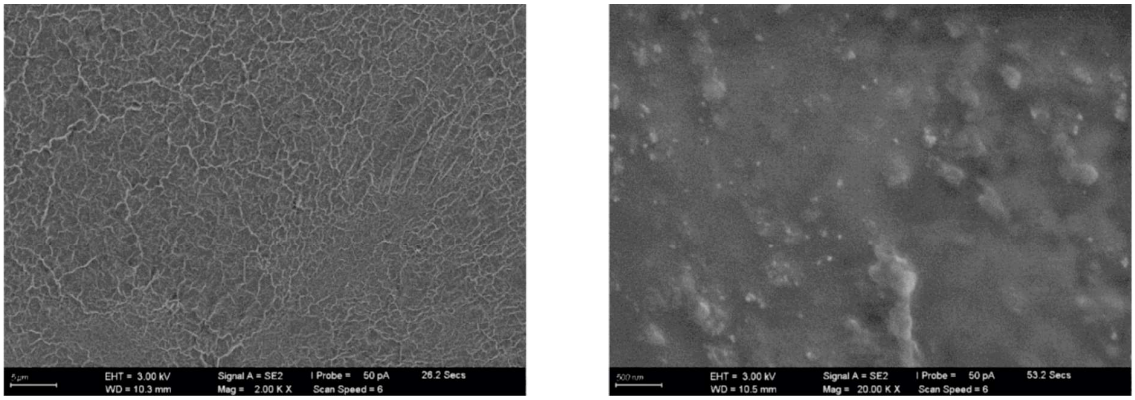


Firgure 1. The XRD pattern and regarding of SEM images

The phase of ZIF-8, mesoZIF-8 and TiO_2@ZIF-8 were shown by XRD and SEM results (Figure 1). In summary, all of them match with the phase of ZIF -8 material compared to relevant studies. It can be found that the crystals of these MOFs were performed clearly under matched observation at some previous works. In detailed, some peaks at 2θ = 7.4°, 10.5°, 12.8°, and 18.2°, in agreement with tetrahedral ZIF-8 planes (001), (002), (112), and (222), respectively. Moreover, the typical hexagon morphology of ZIF-8 was seen in SEM image, while others showed some changes to smaller ball due to adding some modified agents. The size of these crystals also was observed under SEM images, which showed the size are around 529, 243 and 39 nm for ZIF-8, TiO_2@ZIF-8 and mesoZIF-8, respectively. In general, the successful synthesis of ZIF-8 crystals was conducted in this part.

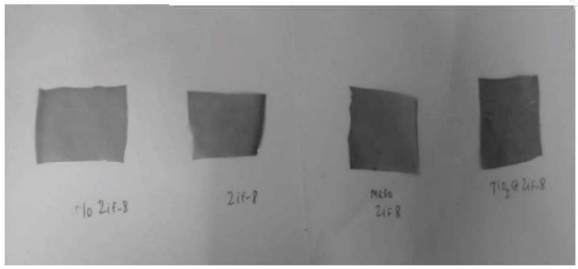
The surface of thin films was observed by SEM and real picture (Figure 2). Comparing of Fig.2a and 2b, it can be concluded that the ZIF -8 was grafted on the polymer in well. In Fig.2a, pure and smooth surface was seen without adding ZIF -8 while Fig.2b showed ZIF-8s crystals on the surface of

polymers with the particle size around 50 nm, agreement to SEM images of the crystals. On the other hand, the real film is soft, good tensibility for all as seen in Figure 3. In fact, the thin film can be used as would healing treatment. The colour of these films change to darker in other pure polymers, ZIF-8, mesoZIF-8 and TiO_2@ZIF-8 thin films, respectively. Moreover, all films can be stand up at normal condition to seven days. The results are well matched to Zhao or Azin, and the films are potential materials for drug delivery application.



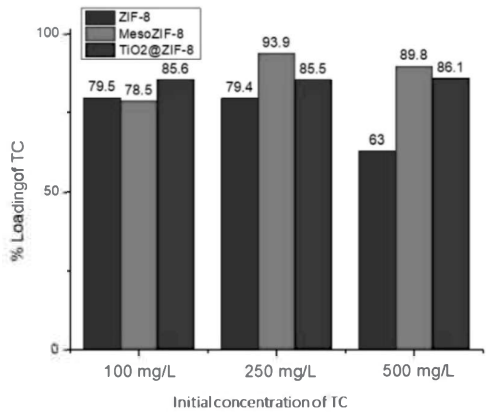
(A) **(B)**

Firgure 2. SEM images of thin films with (a) no ZIF-8 and (b) adding of ZIF-8



Firgure 3. Real pictures of thin films

3.2 TC adsorption and release studies



Firgure 4. Percentage loading of TC versus by initial concentration

The test loading of tetracycline (TC) on ZIF-8 and two derives MesoZIF-8 and TiO_2@ZIF-8 were to carried out as described above (Figure 4). As previous works, the adsorption TC almost reaches the equilibrium state for 24 hours. It was indicated that the ability adsorption proportion in order: MesoZIF-8 > TiO_2@ZIF-8 > ZIF-8 for all experiments. In a low initial TC concentration of 100 mg/L, the TC loading percentage is similar for three samples, achieving over 80%. This high adsorption may be distributed by the good attraction between the amino group of TC and Zn ion from ZIF-8, which formed some attractive bonding. In addition, π-π stacking contributed to the adsorption in these case. However, when increasing TC initial concentration to 250 mg/L, % loading on the mesoZIF-8 sample showed higher than TiO_2@ZIF-8 and ZIF-8. At the initial concentration of TC of 500 mg/L, the percentage of TC loading is 93, 83, and 63 for mesoZIF-8,

TiO_2@ZIF-8, and ZIF-8, respectively. However, the adsorption of TC on mesoZIF-8 and TiO_2@ZIF-8 are the same. It can be speculated that the TC adsorption is relative smaller morphologies of crystals. Herein, the mesoporous one showed a better loaded TC than others, which may have explained by allowing the entrance of bigger molecules inside its structure, then can support much adsorption.

The loaded TC thin films then were tested to determine release capacity. It is known that the slowly and controlling release is better one for drug application. As seen in Figure 5, the TC release of 4 films are different. With film no adding ZIF-8, the concentration of TC is 64% after 1 hour, then up to 72% release all TC after 4 hours. While the thin Film with pure ZIF-8, it gets 45% release after 1h, then proportional increase to 65% after 12 hours. In the other hand, thin film with MesoporeZIF-8 showed a good result: 45% release after 1h, then rapidly increase to 52% and stays in stability. Finally, thin film adding TiO_2@ZIF-8 steady release around 30% for all time. It is found that the best thin film is mesoZIF-8 since it can be controlled the release speed of drug. It can be known that loaded TC on mesoporous thought filling way helps drug release effectively as expected. The film with pure ZIF-8 showed un-controlling release speed while the TiO_2@ZIF-8 thin film cannot release more TC in the same condition. It can be explained that the electrostatic attraction between amine group and cation form adsorbent might be enhanced. Thus, the drug release showed the best thin film, using mesoporous ZIF-8, and the material is a potential candidate for drug delivery application. Finally, the results exhibit potential materials for TC adsorption since this value has considerably been higher than previous relevant reports of ZIF-8 shown in Table 1 and a biocompatibility adsorption process.

Table 1. TC adsorption amount on some MOFs

Materials	TC adsorption amount (mg/g)	Reference
Cu-ZIF-8	307.9	[16]
Fe-ZIF-8	367.0	[21]
ZIF-8 (Hierarchically porous)	574.7	[12]
AC-ZIF-8	35.1	[1]
Fe_3O_4@ZIF-8	402.4	[8]
MesoZIF-8	1484.2	This work
TiO_2@ZIF-8	1014.8	This work

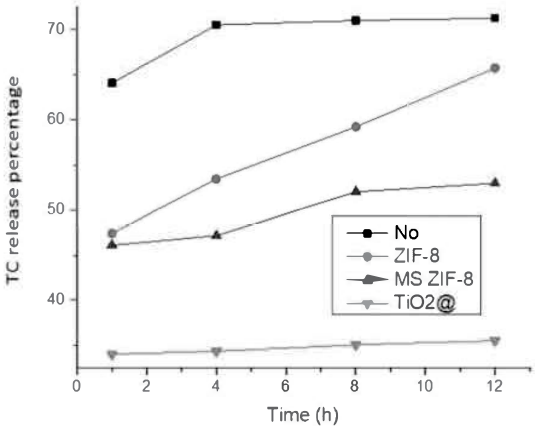


Figure 5. Percentage of TC release versus by time

4. CONCLUSION

In summary, three thin films are synthesised by adding some green agents and ZIF-8s successfully. The structure of ZIF-8 crystals is still maintained after experiments. The ZIF-8s distributes orderly and evenly on the surface of thin films. The TC delivery is tested on these membranes and give expected results. The

mesoZIF-8 thin film shows as a suitable membrane for drug delivery when the speed of drug release can be controlled. The research indicates new way in the application of ZIF-8 thin film for drug delivery.

REFERENCES

Ahmadi, S. A. R., Kalaee, M. R., Moradi, O., Nosratinia, F., and Abdouss, M. (2021). Core–shell activated carbon-ZIF-8 nanomaterials for the removal of tetracycline from polluted aqueous solution. *Adv Compos Hybrid Mater*, vol. 4, no. 4, pp. 1384–1397, DOI: 10.1007/s42114-021-00357-3.

Ge, Y. *et al.* (2022). A ZIF-8-based multifunctional intelligent drug release system for chronic osteomyelitis. *Colloids Surf B Biointerfaces*, vol. 212, p. 112354, DOI: https://doi.org/10.1016/j.colsurfb.2022.112354.

Kaur, H., Mohanta, G. C., Gupta, V., Kukkar, D., and Tyagi, S. (2017). Synthesis and characterization of ZIF-8 nanoparticles for controlled release of 6-mercaptopurine drug. *J Drug Deliv Sci Technol*, vol. 41, pp. 106–112, DOI: https://doi.org/10.1016/j.jddst.2017.07.004.

Kida, K., Okita, M., Fujita, K., Tanaka, S., and Miyake, Y. (2013). Formation of high crystalline ZIF-8 in an aqueous solution. *CrystEngComm*, vol. 15, no. 9, p. 1794, DOI: 10.1039/c2ce26847g.

Lee, Y. R., Kim, J., and Ahn, W. S. (2013). Synthesis of metal-organic frameworks: A mini review. *Korean Journal of Chemical Engineering, 30,* 1667-1680. DOI: 10.1007/s11814-013-0140-6.

Lee, Y. R., Jang, M. S., Cho, H. Y., Kwon, H. J., Kim, S., and Ahn, W. S. (2015). ZIF-8: A comparison of synthesis methods. *Chemical Engineering Journal*, vol. 271, pp. 276–280, DOI: 10.1016/j.cej.2015.02.094.

Li, Y., Zhou, K., He, M., and Yao, J. (2016). Synthesis of ZIF-8 and ZIF-67 using mixed-base and their dye adsorption. *Microporous and Mesoporous Materials*, vol. 234, pp. 287–292, DOI: http://dx.doi.org/10.1016/j.micromeso.2016.07.039.

Liu, H., Chen, L., and Ding, J. (2017). A core-shell magnetic metal organic framework of type Fe_3O_4@ZIF-8 for the extraction of tetracycline antibiotics from water samples followed by ultra-HPLC-MS analysis. *Microchimica Acta*, vol. 184, no. 10, pp. 4091–4098, DOI: 10.1007/s00604-017-2442-6.

Luan Tran, B., Chin, H. Y., Chang, B. K., and Chiang, A. S. T. (2019). Dye adsorption in ZIF-8: The importance of external surface area. *Microporous and Mesoporous Materials*, vol. 277, pp. 149–153, Mar. DOI: 10.1016/j.micromeso.2018.10.027.

Mazloom-Jalali, A., Shariatinia, Z., Tamai, I. A., Pakzad, S. R., and Malakootikhah, J. (2020). Fabrication of chitosan–polyethylene glycol nanocomposite films containing ZIF-8 nanoparticles for application as wound dressing materials. *Int J Biol Macromol*, vol. 153, pp. 421–432, DOI: https://doi.org/10.1016/j.ijbiomac.2020.03.033.

Pan, Y., Liu, Y., Zeng, G., Zhao, L., and Lai, Z. (2011). Rapid synthesis of zeolitic imidazolate framework-8 (ZIF-8)

nanocrystals in an aqueous system. *Chemical Communications*, vol. 47, no. 7, p. 2071, DOI: 10.1039/c0cc05002d.

Peng J. *et al.* (2021). Hierarchically porous ZIF-8 for tetracycline hydrochloride elimination. *J Solgel Sci Technol*, vol. 99, no. 2, pp. 339–353, DOI: 10.1007/s10971-021-05576-0.

Saghir, S., and Xiao, Z. (2021). Facile preparation of metal-organic frameworks-8 (ZIF-8) and its simultaneous adsorption of tetracycline (TC) and minocycline (MC) from aqueous solutions. *Mater Res Bull*, vol. 141, p. 111372, DOI: https://doi.org/10.1016/j.materresbull.2021.111372.

Sheng, G., Dong, H., and Li, Y. (2012). Characterization of diatomite and its application for the retention of radiocobalt: Role of environmental parameters. *J Environ Radioact*, *113*, 108-115. DOI: 10.1016/j.jenvrad.2012.05.011.

Sun, C. Y. *et al.* (2012). Zeolitic imidazolate framework-8 as efficient pH-sensitive drug delivery vehicle. *Dalton Transactions*, vol. 41, no. 23, pp. 6906–6909, DOI: 10.1039/C2DT30357D.

Sun, S., Yang, Z., Cao, J., Wang, Y., and Xiong, W. (2020). Copper-doped ZIF-8 with high adsorption performance for removal of tetracycline from aqueous solution. *J Solid State Chem*, vol. 285, p. 121219, DOI: https://doi.org/10.1016/j.jssc.2020.121219.

Tanaka, S., Kida, K., Nagaoka, T., Ota, T., and Miyake, Y. (2013). Mechanochemical dry conversion of zinc oxide to zeolitic imidazolate framework. *Chemical Communications*, vol. 49, no. 72, pp. 7884–7886, DOI: 10.1039/C3CC43028F.

Vasconcelos, I. B. *et al.* (2012). Cytotoxicity and slow release of the anti-cancer drug doxorubicin from ZIF-8. *RSC Adv*, vol. 2, no. 25, pp. 9437–9442, DOI: 10.1039/C2RA21087H.

Wang, Q., Sun, Y., Li, S., Zhang, P., and Yao, Q. (2020). Synthesis and modification of ZIF-8 and its application in drug delivery and tumor therapy. *RSC Adv*, vol. 10, no. 62, pp. 37600–37620, DOI: 10.1039/D0RA07950B.

Wu, X., Ge, J., Yang, C., Hou, M., and Liu, Z. (2015). Facile synthesis of multiple enzyme-containing metal-organic frameworks in a biomolecule-friendly environment. *Chemical Communications*, *51*(69), 13408-13411. DOI: 10.1039/c5cc05136c.

Yang, H. *et al.* (2021). High-performance Fe-doped ZIF-8 adsorbent for capturing tetracycline from aqueous solution. *J Hazard Mater*, vol. 416, p. 126046, DOI: https://doi.org/10.1016/j.jhazmat.2021.126046.

Zhong, Y., Mu, X., and Cheang, U. K. (2022). High-performance and selective adsorption of ZIF-8/MIL-100 hybrids towards organic pollutants. *Nanoscale Adv*, vol. 4, no. 5, pp. 1431–1444, DOI: 10.1039/D1NA00819F.