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Hydrothermal synthesise of HF-free MIL-100(Fe) for isoniazid-drug by Meta Simon

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OPEN Hydrothermal Synthesize of HF- Free MIL-100(Fe) for Isoniazid-Drug Delivery Meta A. Simon^{1,4}, Erlina Anggraeni^{1,4}, Felycia Edi Soetaredjo^{1,2*}, Shella Permasari Santoso^{1,2}, Wenny Irawaty¹, Truong Chi Thanh³, Sandy Budi Hartono¹, Maria Yuliana¹ & Suryadi Ismadji^{1,2*} Sustainable development of drug delivery materials with good biocompatibility and controlled-release is a popular topic among researchers. In this research study, we demonstrated the potential of the

21 **metal-organic framework**, that is **MIL-100(Fe)**, as a drug delivery platform for

isoniazid (INH). The MIL-100(Fe) was prepared by using the hydrofluoric acid-free hydrothermal method. Several physical measurements

29 **were conducted to** characterize **the MIL-100(Fe)**,

including x-ray diffraction (XRD), scanning electron microscopy (SEM), nitrogen sorption, and thermal-gravimetric (TG). The synthesized MIL-100(Fe) has octahedron-shaped particles with superior properties, that is large surface area (1456.10 m²/g) and pore volume (1.25 cm³/g). The drug loading rate and capacity were determined by means of adsorption kinetic and isotherm. The studied INH@MIL-100(Fe) adsorption system kinetics follow the

5 **pseudo-first-order model**, while **the** isotherm system follows **the**

5 Langmuir model with the maximum adsorption capacity of 128.5 mg/g at 30 °C.

MIL-100(Fe) shows adequate biocompatibility, also exhibits a reasonable and controlled drug release kinetics. The results obtained show that MIL-100 (Fe) can be a good choice of drug delivery platform among other available platforms. Isoniazid (or isonicotinylnhydrazide, abbreviated as INH) is a heterocyclic drug that contains N, which is known for its anti-mycobacterial properties for the treatment of Tuberculosis (TB). INH has been listed by the World Health Organization as an efficacious TB drug and is the first-line barrier to TB. It is known that the mechanism of INH in the treatment TB involves many macromolecular and biosynthesis pathways, especially the synthesis of mycolic acid. The practice of using INH for medicinal purposes began 60 years ago^{1–3}. Despite its efficacy, many experts point out that TB treatment by using INH requires quite long time (i.e., between 6–9 months and in some cases can reach several years). Long-period treatment accompanied by consumption can cause hepatotoxicity and peripheral neuritis, as well as the emergence of drug-resistant species^{4–6}. The long duration of TB treatment is due to the poor solubility and bioavailability of the INH^{7,8}; the controlled drug delivery is one of the strategies to overcome these drawbacks. A controlled and sustained drug delivery system can help to reduce the side effects and increase the efficiency of the treatments. Moreover, it can prevent the emergence of drug-resistance species due to fluctuations in drug content will cause bacteria to lack time to adapt⁹. Several sophisticated biomaterials have been developed to improve the efficiency of drug delivery systems; such as biopolymer, silica, and lipid-based materials. Despite the rapid development of biomaterials for drug delivery systems, the low drugs loading due to the materials small pore volume is still an unsatisfactory aspect¹⁰. Recently, to overcome this drawback, a large pore volume material, namely metal-organic framework (MOF) have been utilized as drug delivery material^{11,12}. MIL-100(Fe) is a MOF which composed of trimesic acid organic linker and Fe-O metal clusters. MIL-100(Fe) can be synthesized using organic solvent and strongly acidic solution such as HF^{13,14}. However, HF is a chemically toxicant, and organic solvent such as DMF or DEF can cause environmental damage in large quantities^{10,15–18}. Jeremias and co-workers revealed that the less toxic HNO₃ could be used to replace HF

7 in the synthesis of MIL-100(Fe). The synthesized MIL-100(Fe)

has a porous structure with a large surface area (~2000 m²·g⁻¹ BET) and pore volume 1Department of Chemical Engineering, Widya Mandala Surabaya Catholic University, Kalijudan 37, Surabaya, 60114, Indonesia. 2Chemical Engineering Department,

15 National Taiwan University of Science and Technology, No. 43, Sec. 4, Keelung Rd, Da'an District, Taipei, 10607, Taiwan. 3Department of Chemical Engineering,

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Figure 1. Schematic diagram of the overall study, including preparation of MIL-100(Fe), drug loading and release. ($\sim 0.9 \text{ cm}^3 \cdot \text{g}^{-1}$)^{11,12,15}. Due to these advantageous

29properties of MIL-100(Fe), it has been proposed as a

potential drug delivery system¹². Another advantage of loading drugs into highly porous materials is the prevention of drug agglomeration during dissolution¹⁹.

5In the present study, **we** investigated the **potential application of MIL-100(Fe)**

to promote the loading and release of INH. Several models for drug loading and release have been implemented and studied. **Materials and Methods** **Materials**. The chemicals used in this study are: trimesic acid (H3BTC; CAS 554-95-0), ferric chloride hexahydrate ($\text{Fe}(\text{Cl})_3 \cdot 6\text{H}_2\text{O}$; CAS 7708-05-0), nitric acid 65% (HNO_3 ; CAS 7697-37-2), isoniazid (INH, $\text{C}_6\text{H}_7\text{N}_3\text{O}$; CAS 54-85-3), and ethanol ($\text{C}_2\text{H}_5\text{OH}$; CAS 64-17-5). Trimesic acid, ferric chloride hexahydrate, and nitric acid were obtained from Merck, Germany. INH, as a drug model, was obtained from Sigma Aldrich, India. Ethanol was purchased as an analytical grade from PT. Indofa Utama Multi-Core, Surabaya, Indonesia. All chemicals were directly

9used as received without further purification. Preparation of MIL-100(Fe).

Figure 1 shows **the**

schematic diagram of the overall study, specifically the preparation of MIL-100(Fe), drug loading, and release study. MIL-100(Fe) was synthesized hydrothermally according to reported procedure, the molar ratio Fe:BTC:HNO₃:H₂O of 1: 0.67:0.6:166 was used for the synthesis. Briefly, all materials were combined in a 100 mL beaker glass. Then, the

13mixture was loaded into a Teflon **autoclave and** heated **at 150 °C for 12 h. The** resulting **MIL-100(Fe)** solid **was**

collected and washed for several times using distilled water. Subsequently, the MIL-100(Fe) solid was purified by soaking in

16water at 80 °C for 1 h, followed by ethanol at 60 °C for 3 h. The purified **MIL-100(Fe)** **was**

dried in a 60 °C oven and heat-activated using a vacuum oven for 2 h at 120 °C.

30Characterization of MIL-100(Fe). The as-synthesized MIL-100(Fe) was characterized by X-Ray Diffraction (XRD), Scanning Electron Microscope (SEM),

Nitrogen (N₂) Sorption, and Thermo-Gravimetric Analysis (TGA). The XRD analysis was carried out in a PW 3064/60 X'PERT-PRO with CuK α ($\lambda = 1.5406 \text{ \AA}$) as the radiation source. The analysis was conducted at 30 mA and 40 kV. The scan range used was 3–20° (2 θ) with the step size of 0.02°. SEM imaging was performed using FESEM-JEOL JSM-6500F to obtain crystal morphology. N₂ sorption measurement was conducted in a Quantachrome at

4–195.6 °C. The surface area of the sample was calculated using the multiple-point Brunauer–Emmett–Teller (BET) equation at p/p₀ range of 0.05–0.3 and total pore volume was determined at the saturated point at p/p₀ = 0.997.

Prior for N₂ sorption measurement,

13MIL-100(Fe) was outgassed at 200 °C for

6 hours. The

20thermal stability of MIL-100(Fe) was analyzed using

Perkin Elmer thermogravimetric analysis (TGA) 8000 in the N₂ atmosphere (20 mL/min) with heating rate 10 °C/min from 29.5 °C to 800 °C. Adsorption isotherm and kinetics. The adsorption kinetics was used to determine the required time for INH loading onto MIL-100(Fe). Briefly, an aliquot of isoniazid (100 mg/L and 120 mg/L) was placed into a series of Erlenmeyer flasks. Subsequently, 0.05 g

26MIL-100(Fe) solid was introduced into the Erlenmeyer flasks. The

flasks were closed and put into a shaker water bath. The adsorption kinetic study was conducted at 30 °C.

6At a specific interval of time, one of the Erlenmeyer flasks was taken to measure the

amount of INH loaded. The adsorption isotherm

11was conducted according to the following procedure: A known amount of MIL-100(Fe) was

11 added into a series of Erlenmeyer flasks containing 25 mL of isoniazid solution. The Erlenmeyer flasks were transferred to a shaker water bath at

200 rpm. The adsorption was done until the equilibrium time was reached (in this case is 5 h, as determined from the

8 kinetic study). The adsorption study was carried out at

30 °C. After the equilibrium condition was achieved, the

6 solid adsorbent was removed from the solution using centrifugation. The concentration of the remaining INH in the solution was measured using spectrophotometric measurement at 262 nm wavelength.

Drug loading and release. A certain amount of INH is dissolved in water, where the concentration of INH used is higher than the maximum loading capacity of MIL-100(Fe) based on adsorption study. Then, 0.05 g

26 MIL-100(Fe) was introduced into the INH solution

in a closed-dark bottle. The loading was done by 200 rpm orbital shaker for 5 h under a constant temperature of 30 °C. The unloaded INH was separated by means of centrifugation, and subsequently the concentration of unloaded INH was determined using spectrophotometer (OD_{262nm}). In vitro release study was done to determine the release profile of INH from MIL-100(Fe). A phosphate buffer saline (PBS) pH 7.4 and 5.8 was used to mimic the blood plasma condition. 0.16 g of INH-loaded MOF, isoniazid@MIL-100(Fe), is added into a 5 mL PBS solution in a dialysis membrane. The INH release was carried out in 80 mL PBS at 37 °C under a slow-constant stirring. At a 1 h time interval, 2 mL of solution was taken to measure the released-INH isoniazid by means of UV spectrophotometric; at the same time, 2

22 mL of fresh PBS solution was added into the system. The

cumulative %release (R) of INH is calculated by using the following equation: $R(\%) =$

$$\frac{\sum \text{Conc}_{\text{INH-detected}}(\text{mLg}) \times \text{Volsystem}(\text{L})}{\sum \text{mass}_{\text{sampling}}(\text{mg}) + \sum \text{mass}_{\text{modified-MIL100}}(\text{mg})} \times 100\%$$

(1) $\text{mass}_{\text{sampling}}(\text{mg}) = \text{Conc}_{\text{INH-detected}}(\text{mLg}) \times \text{Volsampling}(\text{L})$ (2) Result and Discussion

Synthesis and characterization of MIL-100(Fe). The metal-organic framework (MOF) MIL-100 (Fe) is synthesized from the coordinated iron (Fe) trimers and trimesate ligands. The

10 MIL-100(Fe) has a super tetra-hedron structure,

as depicted in Fig. 2. The coordination of diamond-like shapes MIL-100(Fe) particles produces small pore opening, in each cell unit²⁰. Upon activation, the pore size can reach 29 Å and 24 Å for each large and small pore, respectively^{14,21}.

14For comparison purposes, the synthesized MIL-100(Fe), from this study, was

characterized using XRD, SEM, N₂ sorption, and TGA.

21The XRD crystallinity pattern of synthesized MIL-100(Fe) from this study and

from literature is shown in Fig. 3; it is observed that both XRD patterns are in a good agreement¹⁸. The 2θ peaks and the corresponding lattice of MIL-100(Fe), from this study, are observed at 3.4° (220), 4.0° (311), 4.8° (400), 5.3° (331), 5.9° (422), and 6.3° (333). Calculations by using Miller indexing and Bragg's law indicate that the synthesized

14MIL-100(Fe) has a cubic structure with

a lattice parameter of 73 Å; which is in accordance with a previous report^{21,22}. The SEM micrographs were collected to confirm the morphology of

1MIL-100(Fe). As shown in Fig. 4, MIL-100(Fe)

has an octahedron shape which belongs to the cubic (isometric) crystal; this is in accordance with the structure suggested from XRD. Also, from the SEM images, some small irregular-shaped particles can be observed, which is probably the MIL-100(Fe) whose structure collapsed. Enormous surface and large pore volume are distinguishing properties of MOFs; these two properties are measured by using

7N₂ adsorption-desorption isotherm for the synthesized MIL-100(Fe).

The N₂-sorption isotherm curve is shown in Fig. 5. As derived from the sorption data, the

23BET surface area and pore volume of MIL-100(Fe) are 1456.10 m²/g and 1.25 cm³/g, respectively;

this result is quite similar to that of reported MIL-100(Fe) in Table 1. The N₂-sorption curve of MIL-100(Fe) indicates a combination of

24type I and IV with a narrow hysteresis loop in the relative pressure (P/P₀) range of 0.6 to 1.0.

The rapid intake of N₂ gas at relatively low P/P₀ indicates that MIL-100(Fe) possesses both microporous and mesoporous cages^{23,24}. The reported drug delivery materials (i.e., MSN8, MSN5, beta zeolites, and MCM-41) are shown in Table 1; it is well noted that the

7MIL-100(Fe) possesses higher surface area and pore volume,

which is more favorable to facilitate drug loading. The

20thermal stability of MIL-100(Fe) was investigated by using thermogravimetric analysis; **the**

resulting TG curve is shown in Fig. 6. The MIL-100(Fe) exhibits 3 stages weight loss; that is at temperature range of 60–340 °C with 5% weight loss, at 340–400 °C with 34.20% weight loss, and at 400–680 °C with 38.90% weight loss. The first stage thermal degradation is corresponding to the removal of trapped water molecules followed by mild decomposition of O-containing functional groups. A minimal weight loss (almost plateau) at the first stage also indicates that the MIL-100(Fe) is stable up to this range of temperature. Substantial weight loss was observed above temperature of 340 °C; this is due to the structural collapse of the MIL-100(Fe) as the ligand was decomposed. The subsequent drastic mass reduction started at 400 °C, which is caused by the continuous decomposition of the framework accompanied by the reduction of the iron^{25,26}. The third stage degradation ends up to 680 °C, which also indicates that MIL-100(Fe) is completely decomposed. Adsorption kinetic. The adsorption rate of INH, with MIL-100(Fe) as host adsorbate, was studied kinetically to find the equilibrium adsorption time. The adsorption

27kinetics was represented by the pseudo-first-order (Eq. 3) and the pseudo-second-order equations (Eq. 4),

which has the mathematical forms as following²⁷: Figure 2. Illustrated

31crystal structure of MIL-100(Fe). 220 311 Cubic

or isometric crystal Intensity 333 400 422 331

31MIL-100(Fe), this work MIL-100(Fe),

Ref. [18] 4 6 8 10 12 14 16 18 20 2θ Figure 3. X-ray diffraction pattern

5 of MIL-100(Fe). Figure 4. SEM image of the synthesized MIL-100(Fe).

1000 800 Volume (cm³/g) 600 400 200 0 0.0 0.2 0.4 0.6 0.8 1.0 P/P₀ Figure 5. Nitrogen adsorption-desorption isotherm of

9 MIL-100(Fe). Material MSN8 BET surface area (m²/g) 715 Pore volume (cm³/g) 1.

697 Ref. 37 MSN5 650 1.229 37 Beta zeolites 513 0.23 38 MCM-41 1506 Not available 39 MIL-100(Fe) 1190–1520 0.69–0.93 40 MIL-100(Fe) 1835 1.23 41 MIL-100(Fe) 1456.10 1.25 This study Table 1.

Comparison of

10 BET surface area and pore volume of MIL-100(Fe)

with other porous materials. MSN8 = mesoporous silica nanoparticles with pore size 8.2 nm; MSN5 = mesoporous silica nanoparticles with pore size 5.4 nm; Beta zeolites = Al₂O₃:2 SiO₂:TEA₂O:30 H₂O; MCM-41 = mobil composition of matter no. 41, a mesoporous silica material. $qt = q_e(1 - e^{-k_1t})$ $qt = (1 + q_e k_2 t) e^{-k_2 t}$ (3) (4)

17 where, q_e and q_t (mg/g) are the amount of INH adsorbed on MIL-100(Fe) at equilibrium and at time t (hours), respectively. The k_1 and k_2

are the pseudo-first-order and pseudo-second-order adsorption constant, respectively. Often, k_1 and k_2 called as time constant. The adsorption kinetic curve built from the experimental data was presented in Fig. 7, while the calculated parameters are summarized in Table 2. The experimental data show that the adsorption equilibrium time was reached after 5 h. The pseudo-first-order and pseudo-second-order model equation were used for data fitting. The curve fitting shows that the pseudo-first-order model can correlate the calculated and experimental data better than that of pseudo-second-order. Moreover, the q_t value found from pseudo-first-order fitting was closer to that of experimental results. The sum square error (SSE) of the data was also calculated; it 110 100 d d 5% 90 %weight 34.2% 60 d d 38.9% d 80 70 50 40 30 0 100 200 300 400 500 600 700 800 Temperature, °C Figure 6. The thermogravimetric curve of MIL-100(Fe). 120 100 80 q_t (mg/g) 60 40 INH 100 ppm 20 INH 120 ppm Pseudo 1st order Pseudo 2nd order 0 0 1 2 3 4 5 6 time (hours) Figure 7. Adsorption kinetics curves of INH@MIL-100(Fe) system. Model Parameters k_1 , g/mg·h Initial concentration, mg/L 100 1.040 ± 0.095 120 0.719 ± 0.044 Pseudo 1st order q_e , mg/g 92.681 ± 2.678 110.271 ± 2.257 R² 0.994 0.998 k_2 , g/mg·h 0.010 ± 0.249 0.005 ± 0.091 Pseudo 2nd order q_e , mg/g 110.631 ± 20.688 138.898 ± 8.864 R² 0.970 0.994 Table 2. Adsorption kinetics of INH@MIL-100(Fe). is obtained that the SSE of pseudo-first-order and pseudo-second-order successively is 4.089 and 6.188. The values of R² for pseudo-first-order are 0.994 for 100 mg/L and 0.998 for 120 mg/L, which is higher than R² from pseudo-second-order (0.970 for 100 mg/L and 0.994 for 120 mg/L). The error analysis also indicates that the pseudo-first-order model

6 could represent the experimental data better than the pseudo-second order

equation. onto MIL-100(Fe)²⁸. The adsorption rate decreases as the INH concentration is increased, this may be due to the The value of $k_1 > k_2$ suggests that intra-particle diffusion (IPD) is the rate-limiting in the adsorption of INH higher probability of collision (at high concentration) so that the IPD is inhibited.

Adsorption isotherm. Adsorption isotherm study was conducted to determine the loading capacity MIL-100(Fe) against INH. The adsorption isotherm is represented by the Langmuir and Freundlich models, with mathematical models as following²⁹: $q_e = (1 + mKKLCLCee)$ (5) 140 120 100 q_e (mg/g) 80 60 40 20 0 C_e vs q_e Langmuir Freundlich 0 50 100 150 200 250 C_e (mg/g) Figure 8. Adsorption isotherm curve of INH@MIL-100(Fe) system. Model Parameter KL, L/mg Value 0.056 ± 0.006 Langmuir q_m , mg/g 128.518 ± 0.687 R² 0.996 KF, (mg/g)(L/mg)^{1/n} 40.776 ± 5.061 Freundlich n 0.207 ± 0.027 R² 0.989 Table 3.

8 Adsorption isotherm of INH @MIL-100(Fe).

$q_e = KFCe^n$ (6) where, KL and q_m are the Langmuir constant and maximum adsorption capacity (mg/g), respectively.

28 KF ((mg/g) (L/mg)^{1/n}) and n are the Freundlich constants. The adsorption isotherm curve of

INH

8 @MIL-100 (Fe) system is shown in Fig.

8. A steep increase from q_e was observed to $C_e \pm 50$ mg/g; almost a plateau was observed later

7 which indicated that the maximum adsorption capacity

almost reached. The fitting parameters of the Freundlich and Langmuir models are given in Table 3, from R² value it was evident that Langmuir could represent the experimental data better than the Freundlich. The superiority of Langmuir over Freundlich equation due to the system has saturation capacity at high C_e . Based on the isotherm measurement, approximately 128 mg of INH can be loaded onto MIL-100(Fe). Drug kinetic release. The in vitro drug release is conducted to study the INH release. A PBS solution was used as the release medium to simulate the biological condition. Two different release pH of 5.8 and 7.4 were considered to mimic the intestine pH and blood pH, respectively³⁰.

12 The total INH content was determined by gently stirring the INH @MIL-100(Fe) in PBS for 24 h, then the concentration of INH released into the

PBS solution

9 was determined by using UV spectroscopy method. The release profile data of

INH@MIL-100(Fe) are shown in Fig. 9. There is no burst effect occurred during the INH release in PBS solution at both pHs; this

12 indicates that MIL-100(Fe) can be a potential biocompatible drug

release platform. The kinetic release was represented as the % cumulative release (R). Then, R was fitted to zero-order (Eq. 7)³¹, first-order (Eq. 8)²³, and Higuchi (Eq. 9)³¹ model: $R = q_0 + k_0t$ (7) $R = R_e(1 - e^{-kt})$ (8) $R = kHt^{0.5}$ (9) where, k_0 , k , and kH are the kinetic constant of zero-order (mg/g·h), first-order (1/h), and Higuchi (%/h^{0.5}) model, respectively. The parameter R_e , q_0 , and t represent the % release of INH at equilibrium time, initial amount of INH in PBS (mg/g), and release time (h), respectively. Later on, a good fitting to the zero-order model indicates that the release system is a transdermal and osmotic system. A good fitting to the first-order model describes the release system of water-soluble drugs in a non-swelling porous matrix³². While a good fitting to Higuchi model indicates drug release from a planar heterogeneous matrix system by passing through the pore matrix³³. 100 80 60 R (%) 40 t vs pH 5.8 t vs pH 7.4 20 Zero order First order Higuchi 0 0 5 10 15 20 25 time (hours) Figure 9. The drug release profile of INH

25 @MIL-100(Fe) system, at pH 5.8 and pH 7.4.

Figure 10. Cell viability assay of MIL-100(Fe) at different concentrations and certain incubation period. Model

22 Parameters pH 5.8 pH 7.4 Higuchi kH ,

%/h^{0.5} 10.748 ± 0.829 14.356 ± 1.339 R² 0.978 0.970 k_0 , mg/g·h 1.834 ± 0.188 2.472 ± 0.271 Zero Order R_e , mg/g 12.020 ± 2.415 15.969 ± 3.442 R² 0.8732 0.865 R_e , % 53.037 ± 0.734 72.289 ± 1.345 First Order k , 1/h 0.120 ± 0.004 0.122 ± 0.005 R² 0.997 0.995 Table 4. Release kinetic of INH@MIL-100(Fe). The model fitting into the release profile data of INH

7 @MIL-100(Fe) is shown in Fig. 9, and the

fitted parameters are summarized in Table 4. The error analysis of SSE and R² show

18 that the release profile of INH @MIL-100(Fe) is

better represented by the first-order model, which typical for a drug release system from porous matrices. This suggests that the release mechanism is a continuous-controlled release system with different release rates⁹. Moreover, from experimental data, the R-value for release system at pH 5.8 and pH 7.4 (after 24 h) is found to be 50.38% and 72.22%, respectively. Meanwhile, the Re (and k) value calculated from the first-order model is found to be 53.037% (0.120/h) and 72.289% (0.122/h), for pH 5.8 and 7.4, respectively. Both experimental and calculated result shows a good agreement. The release of INH is better in alkaline pH because in this condition there are more negatively charged molecules (from water) that can bind to the metal cluster of MIL-100(Fe), this will cause interference for interactions between the INH molecules and MIL-100(Fe) active surface. Some release profile of MIL-100(Fe) and modified MIL-100(Fe) against several drugs are presented in Table 5. Based on the collected data, there is still no release data reported for INH@MIL-100(Fe) system. In comparison with other drug release study,

18it can be seen that the MIL-100(Fe) prepared in

this study can match almost all reported release data. Material MIL-100(Fe) Drug model TP Release medium Gamble's solution Cumulative release ~58% (48 h) Ref. 36 Fe₃O₄@MIL-100(Fe) DOX PBS pH 7.4 53.5 mg/g (25 days) 42 MIL-100(Fe) AAS IBU Deionized water 99% (AAS, 3 days) 84% (IBU, 3 days) 43 Polypyrrole@MIL-100(Fe) DOX PBS buffers 42.7% (pH 7.4, 24 h) 82.7% (pH 5.0, 24 h) 44 MIL-100(Fe) ACF Phosphate buffer pH 6.8 91% (30 h) 45

25Zn II-MIL-100(Fe) ACF Phosphate buffer pH 6.8

75% (72 h) 45 MIL-100(Fe) TC DOXc Simulated gastric fluid 96% (TC, 48 h) 81% (DOXc, 48 h) 46 MIL-100(Fe) INH PBS 50.38% (pH 5.8, 24 h) 72.22% (pH 7.4, 24 h) This study Table 5. Release profile comparison of MIL-100(Fe) and its modified form against different drug. TP = Theophylline, DOX = Doxorubicin hydrochloride, AAS = Aspirin, IBU = Ibuprofen, ACF = Aceclofenac, TC = Tetracycline, DOXc = Doxycycline, INH = Isoniazid. Biocompatibility assay. Safe drug delivery materials must have little or no toxic effect on normal cells. In this study, an MTT assay on mouse osteoblast cells 7F2 was used to test the biocompatibility of the drug delivery material, that is MIL-100(Fe). MIL-100(Fe) at particular concentration (25, 50, or 100 µg/mL) was introduced to the cell culture and incubated for periods of 12, 24, and 48 h (Fig. 10). The detail of the procedure can be seen elsewhere³⁴. Relatively high cell viability (up to 83%, after 24 h incubation; and ~79%, after 36 h incubation) was maintained by using 25 µg/ mL of MIL-100(Fe) which shows biocompatibility of this material, at this concentration³⁵. It was observed that cell viability was decreased significantly at higher MIL-100(Fe) concentrations, also the prolonged incubation times lead- ing to cell toxicity. This indicates that MIL-100(Fe) should not be administered at concentrations of more than 25 µg/ mL due to its cytotoxic effect (Fig. 10). Cytotoxicity of MIL-100(Fe) may be caused by the presence of Fe metal which triggers the generation of reactive oxygen species that can cause cell damage³⁶. In addition, the presence of metals (in metal-organic materials) increases the ability to penetrate into the cells thus induce more severe tissue damage. Conclusion The

10metal-organic framework, namely MIL-100(Fe), has been successfully synthesized

using the hydrothermal method. The as-synthesized

14 MIL-100(Fe) has a cubic crystal structure with a large surface area and

pore volume which can facilitate drug loading. The characteristics

8 of the synthesized MIL-100(Fe) is in good agreements with the reported characteristics. The adsorption study of INH onto MIL-100(Fe)

indicates that intra-particle diffusion was the rate-limiting in the system. The maximum uptake of INH@IL-100(Fe) is found to be 128.5 mg/g based on Langmuir model; which represents the approximate drug loading capacity

5 of MIL-100(Fe). Based on the release profile, MIL-100(Fe) show a

good controlled-release of INH and there is no burst observed during the release. Furthermore, the MIL-100(Fe) itself show a good biocompatibility. All of these findings imply that MIL-100(Fe) is a promising drug delivery platform for INH. Received: 17 August 2019; Accepted: 24 September 2019; Published: xx xx xxxx

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19Competing interests The authors declare no competing interests. Additional information **Correspondence and requests for materials should be addressed to F.**

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