Synthesis and Characterization of $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}$ Nanocomposite as Antibacterial Drug Nanocarrier Agent

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Research Article

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Abstract

Metal-organic frameworks (MOFs) are developing as a powerful platform for the delivery and controlled release of drugs. In this study, we reported a novel magnetic framework including $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}$ for the delivery of tetracycline (TC) antibiotic. The obtained results of this research showed that 88% of the TC was loaded on the $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}$. The drug release study was performed in pH: 7.4 and pH: 5.0 which showed 75% and 83% release within 3 days. Moreover, antibacterial activities tests based on well agar diffusion were performed against *Staphylococcus aureus* and *Escherichia coli* bacteria which exhibited satisfactory antibacterial properties of TC-loaded $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}$. Moreover, the prepared structures including $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}$ and $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}/\text{TC}$ were identified using Fourier-transform infrared spectroscopy (FT-IR), energy-dispersive X-ray spectroscopy (EDX), X-ray diffraction (XRD), Scanning electron microscope (SEM) and thermal gravimetric analysis (TGA).

1. Introduction

Nanoparticles (NPs) have received a lot of attention for their biomedical applications including diagnosis of diseases, cancer therapy, and drug delivery systems (DDSs) [1, 2]. DDSs are one of the most promising applications for human health care. An effective drug delivery system is necessary for moving the active drug to the place in question so that the drug can be effective at a special time and place. New drug delivery systems based on nanoparticles enable more effective therapy compared to traditional medication. For these reasons, in recent years, targeted drug delivery system based on nanoparticles has been extensively researched. An ideal drug loading system should have the following: have a large loading capacity, biocompatible, they should be nontoxic or have low toxicity and should be easily degraded by the body's metabolism [3, 4]. Various kinds of nanostructures including liposomes, polymersomes, dendrimers, micelles, nanocapsules, hydrogels and metal-organic frameworks (MOFs), have been used as nanocarriers [5–11].

In recent years, one of the most desirable materials that have drawn great attention is MOFs, which consist of metal ions linked together by organic bridging ligands [12]. The great properties of MOFs, such as simple synthesis, excellent porosity, tunable size and facile modification, high agent loading, and improved biocompatibility, make them promising candidates as drug delivery hosts [13–16]. Among the MOFs, MILs (Materials of institute Lavoisier) are developed because of their interests in DDSs [17, 18]. They have mesoporous structure which makes MILs them potential materials for DDSs due to large surface areas, high loading capacity and capability to control the release of the drug [19]. Also, MILs have displayed stability of its framework in biological fluids for long periods. Recently, different MOFs such as UiO-66 [20], ZIF-8 [21], MIL-100 (Fe) [22], have been used for carrying drugs such as doxorubicin, Acyclovir and doxycycline.

Another material of interest is magnetic nanoparticles (MNPs) that have many applications in various fields such as; biomedicine, magnetic resonance imaging, and catalysis [23–25]. Magnetic drug targeting is an effective way to release the medicine at a special place that could be attained by inserting a

magnetic compound in the drug delivery system [26, 27]. The combination of functional MNPs with MOFs results in the formation of magnetic frameworks composites (MFCs) to improve their properties [28].

One of the most promising materials in biomedical applications is MFCs which have some essential characteristics such as the surface area of these materials are high and porous which allow loading considerable amount of active molecules, they have uniform size pore and diverse chemistry, they are also naturally biodegradable, they show a reasonable response to the stimuli which help them to deliver drugs to target organs, the responsivity of these materials to external stimuli is proper which can be decisive in releasing drugs. As a result, MFCs have been in the center of attention because of their large number of applications in this field [29, 30].

Tetracycline (TC) is a broad-spectrum antibiotic. They are a family of bacteriostatic antibiotics and are used to treat some bacterial infections. Tetracyclines inhibit protein production, they are able to inhibit bacterial protein synthesis by binding reversibly to ribosomal units [31].

Herein, we were able to synthesize a novel core-shell nanocomposite containing $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}$. The antibiotic drug (TC) was then loaded into the nanocarrier within 5 days.

Subsequently, drug release was carried out at the physiological body pH (pH:7.4) and pH:5. The results showed that the TC loading on the nanocomposite was 88%, and the drug release were 75% and 80% at pH:7.4 and pH:5, respectively. In addition, antibacterial properties of drug-loaded nanostructures were compared with pure TC against *Escherichia coli* and *Staphylococcus aureus* bacteria by agar well diffusion method and showed excellent and substantial results (Scheme 1).

2. Experimental

Chemicals were purchased from the Sigma-Aldrich and Merc in high purity. All of the materials were of commercial reagent grade and were used without further purification. FT-IR spectra were recorded on Magna-IR spectrometer 550. Powder X-ray diffraction (XRD) was carried out on a Philips diffractometer of X'pert Company with mono chromatized Cu K α radiation ($\lambda = 1.5406 \text{ \AA}$). Microscopic morphology of products was visualized by scanning electron microscopy (SEM) (LEO 1455VP). The compositional analysis was done by energy dispersive analysis of X-ray (EDX, Kevex (Newark, DE) Delta Class I). Thermogravimetric analysis (TGA) was performed on a Mettler Toledo TGA under argon and heated from room temperature to 825°C. The approximate sample weight was 10 mg in TG experiment with 10°C/min heating rate. Nitrogen adsorption-desorption isotherms were measured at 196°C using a Belsorp mini automatic adsorption instrument after degassing the samples at 150°C for 5 h. Absorption spectra were recorded in the range 200–800nm on a Shimadzu model 1601 PC UV-visible spectrophotometer (Shimadzu, Tokyo, Japan)

2.1. Preparation of MgFe_2O_4 nanoparticles

A mixture of MgSO_4 (1.2 g) and $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (2.4 g) were dissolved in deionized water (30 mL) was stirred until to afford a clear mixture (Solution A). Then, 3.2 g of NaOH was solved in 15 mL of deionized water by a magnetic stirrer, this solution was labeled as mixture B. Then, the solution B was gradually added to the solution A, which followed under vigorous stirring. Eventually, the solution was transferred in stainless steel pressure vessel. The autoclave was kept at 180°C for 10 h and then cooled down slowly. The obtained residue was collected, washed three steps with deionized water, dried and then calcined in a furnace at 700°C for 3 h [32].

2.2. Preparation of $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}$ nanocomposite

$\text{Al}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (1.3 g), 1,4-benzenedicarboxylic acid (0.288 g), MgFe_2O_4 (0.1 g) and deionised water (5 mL) were placed in a 50 mL Teflon-lined steel autoclave and heated at 220°C for 72 h. After completion of reaction, the autoclave was cooled down to room temperature and the powder formed was filtered and washed several times with distilled water and then dried at 45°C for 24 h.

2.3. Drug loading

To incorporate TC into the $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}$, 0.1 g of TC was dissolved in 5 mL of deionized water and then 0.05 g of $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}$ nanocomposite was added. The mixture was sealed tightly and stirred at room temperature for 5 days. After completion of the loading, the prepared $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}/\text{TC}$ was washed three times with deionized water to remove unabsorbed TC. Then dried in an oven at 60°C for 24 h. The amount of drug loading was 88 % based on the Eq. 1:

Drug loading (%) = (TC weight in sample/total weight of sample) $\times$ 100%

2.4. Drug release

The drug release was performed in phosphate buffer saline (pH:7.4) and acetate buffer (pH:5). In this method, 0.02 g of $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}/\text{TC}$ was separately added to 50 mL of each buffer. Then, the solution was stirred at 37°C for 3 days. Each time, 5 mL of the solution was removed and then was quickly replaced with the same amount of fresh buffer.

The amount of drug release from nanocomposite was investigated by a UV-Vis spectrometer at 360 nm. Finally, release percentage was expressed by Eq. 2:

Release percentage (%) = m_r (amount of released TC) / m_l (total amount of loaded TC)

2.5. Antimicrobial Assay

S. aureus and *E. coli* were used as standard strains in this study. To determine the susceptibility of the microorganisms, antibiotics were used from Muller–Hill Agar culture media [33]. Initially, a concentration of (10 µg/mL) of the substance was prepared in 0.01 mol/ml of HCl. After culturing bacteria, the plates were placed at 37°C for 12 h. Then, concentrations of 50, 100, 150 µl of $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}$ and

MgFe₂O₄@MIL-53(Al)/TC were injected into the well. Finally, the plates were incubated at 35°C for 24 hours and the zone of inhibition was measured (mm).

3. Results And Discussion

3.1. Structure Elucidation of MgFe₂O₄@MIL-53(Al) and MgFe₂O₄@MIL-53(Al)/TC

In the preliminary experiments MgFe₂O₄@MIL-53(Al) and MgFe₂O₄@MIL-53(Al)/TC were prepared and characterized by energy-dispersive X-ray spectroscopy (EDX), scanning electron microscopy (SEM), X-ray powder diffraction (XRD), Fourier-transform infrared spectroscopy (FT-IR) and thermal gravimetric analysis (TGA).

The XRD patterns of MgFe₂O₄@MIL-53(Al)/TC confirmed the formation and maintenance of crystallite structure of magnetite nanoparticles. Peaks of MgFe₂O₄ existed at 2θ value of 30.1°, 35.2°, 43.1°, 57.0° and 62.6° [34].

The diffraction patterns of the synthesized MIL-53(Al) samples show high crystallinity with reflections in the 2θ range of 5° – 35° which are characteristics of MIL-n type MOFs [35], XRD related to MgFe₂O₄@MIL-53(Al)/TC showed that the synthesized material was strongly crystalline (Fig. 1).

SEM images of the nanocomposite before and after drug loading are shown in (Fig. 2). The image of the MgFe₂O₄@MIL-53(Al) indicates that the particles have regular and spherical shape.

After loading, the increased size and irregular shape for the MgFe₂O₄@MIL-53(Al)/TC (Fig. 2b), due to the existence of tetracycline with bulk particles compared with MgFe₂O₄@MIL-53(Al).

By EDX measurement we can determine the organic content in the structure of the catalyst. The EDX spectrum of MgFe₂O₄@MIL-53(Al) includes C, O, Al, Fe, Mg elements (Fig. 3a). Furthermore, the EDX spectrum of MgFe₂O₄@MIL-53(Al)/TC contains C, O, Al, Fe, Mg and N elements, which means that tetracycline is loaded on MgFe₂O₄@MIL-53(Al) (Fig. 3b).

The FT-IR spectra of MgFe₂O₄@MIL-53(Al) and MgFe₂O₄@MIL-53(Al)/TC are shown in (Fig. 4). The FT-IR spectra of the synthesized MgFe₂O₄@MIL-53(Al) are shown in (Fig. 4a), The available peak in 594 cm⁻¹ is for the Mg-O bond. exhibited vibration bands in the region 1400–1700 cm⁻¹ for the carboxylic functional group [36]. The bands at 1601 and 1508 cm⁻¹ corresponds to –COO asymmetric stretching whereas the bands at 1435 and 1414 cm⁻¹ attributed to –COO symmetric stretching. The additional absorption band at 1669 cm⁻¹ in the MIL-53(Al) was due to –COOH group of BDC.

As the TC was loaded in MOF carriers, the bands at 1439 cm^{-1} appeared, corresponding to the stretching modes of aromatic carbon C–N bonding. Furthermore, the peak at 1624 cm^{-1} refers to the carbonyl group of the drug. Also observed at 3167 cm^{-1} ascribed to N–H symmetric stretching mode (Fig. 4b).

The thermal stability was probed with thermo gravimetric analysis. TGA curve of $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}/\text{TC}$ (Fig. 5) shows a 5% weight loss due to the evaporation of all solvents in the range of $0\text{--}200^\circ\text{C}$. Moreover, the weight loss (20%) starting from 200°C to 300°C is attributed to the destruction of tetracycline. The MIL-53(Al) MOFs was observed at the range of 300°C to 450°C .

3.2. Study on drug release

Before the release, different concentrations of the drug were prepared in two buffer (phosphate buffer and acetate buffer) solutions. Their absorptions were achieved by a UV-Vis device at 360 nm. Then, their calibration curves were plotted. The drug release diagram at pH: 7.4 and pH: 5 is shown in Fig. 7. As indicated, the structure of $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}$ is unstable in acidic buffer (pH: 5) and degraded very rapidly. For this reason, drug release at pH: 5 is much faster than pH: 7.4 which it's unsuitable for a desirable drug delivery system. The obtained results show that the rate of drug release at pH: 5 increased to 70% during in the first 4 h. Whereas, the release of the drug at physiological of the body (pH:7.4) was about 75% over 72 h and then fixed to be. Based on these observations, the TC release of $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}$ is controlled at pH 7.4.

3.3. Antibacterial activity

The antibacterial activity of TC, $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}$ and $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}/\text{TC}$ against *S. aureus* and *E. coli* were evaluated by using the agar well diffusion method. Concentration of 100 μl showed the best results, as shown in (Fig. 7). Considerable antibacterial activity was observed in the $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}/\text{TC}$ synthesized material. The halo created on *S. aureus* was 18mm for the TC drug and the 29 mm for the drug loaded on the MOF, Also, for the *E. coli* bacterium, it was 18 mm and 21 mm, respectively (Table 1). According to the results, the $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}/\text{TC}$ makes the antibacterial effect of the pure drug much higher.

Table 1
The antibacterial activity of TC, $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}$, $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}/\text{TC}$

Bacterium	TC	$\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}$	$\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}/\text{TC}$
<i>E.coli</i>	18	0	21
<i>S.aureus</i>	18	0	29

Conclusion

In the present work, we have successfully synthesized a novel nanocomposite including $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}/\text{TC}$. In addition, the antibacterial drug (TC) was encapsulated in $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}$ with high loading of 88%. In addition, the drug release from the nanocomposite was carried out at physiological pH of the body (pH:7.4) and pH:5. The results showed that the releases of TC at pH: 7.4 and pH:5 were 75% and 80%, respectively. Finally, to appraise the antibacterial activity of $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}/\text{TC}$ the results of using agar well diffusion method indicated that the antibacterial activity of $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}/\text{TC}$ is more than $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}$ and TC.

Declarations

Acknowledgments

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Conflict of Interest

The authors declare no conflict of interest.

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Figures

Figure 1

X-ray diffraction of MgFe₂O₄@MIL-53(Al)/TC

Figure 2

FE-SEM images of (a) $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}$, (b) $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}/\text{TC}$

Figure 3

EDX analysis of (a) $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}$, (b) $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}/\text{TC}$

Figure 4

FT-IR spectrum of (a) MgFe₂O₄@MIL-53(Al), (b) MgFe₂O₄@MIL-53(Al)/TC, (c) TC

Figure 5

TGA curve of the MgFe₂O₄@MIL-53(Al)/TC

Figure 6

The release of TC from $\text{MgFe}_2\text{O}_4@\text{MIL-53(Al)}$ in two buffers at pH: 5 and pH: 7.4

Figure 7

Results of antibacterial test (a) disk containing *E. coli* bacteria and (b) disk containing *S. aureus* bacteria.

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