Alginate-Coated MIL-100-Fe as an Appropriate Drug Delivery System

Tahereh Azizi Vahed, Mohammad Reza Naimi-Jamal*, Leila Panahi

Department of Chemistry, Research Laboratory of Green Organic Synthesis & Polymers, Iran University of Science and Technology, Tehran 1684613114, Iran

Email: naimi@iust.ac.ir

Abstract

Metal-organic frameworks (MOFs) are a class of crystalline porous materials which contain metal ions and organic linkers in their structure. These materials are known as molecular cages which can trap a various range of molecules and whereby are highly functional in different fields of chemistry.

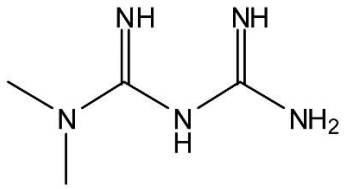
In this work, we exerted coated-nanoporous MIL-100-Fe MOF as a drug delivery system (DDS) to encapsulation and release of a model pharmaceutical agent. The MOF has been prepared using solvothermal technique and then coated with Sodium Alginate as a green biodegradable polymer. Herein Metformin is utilized as a model drug to be trapped inside the MOF pores within an aqueous solution in the presence of the MOF nanoparticles. Metformin is an oral antihyperglycemic agent which is used for the treatment of type II diabetes. The successful synthesis of the framework is proved by several techniques including IR, PXRD, and TGA. In vitro studies showed that this framework is a promising DDS for the targeting and controlling release of drug molecules especially the oral one. By this technique, unwanted effects of the immature release of the loaded drug will be reduced and the drug cargo will be released in a controlled way either which it resulted in the increase of drug bioavailability.

1. Introduction

In the field of drug therapy almost in all cases, a considerable dose of therapeutic agent is needed to initiate a desirable pharmacokinetics process; which resulted in an increase of potential side effects. Drug

delivery systems by encapsulating the pharmaceutical molecules paved the way to eliminating these deficiencies which lead to drug release in a controlled manner.[1] One group of organic-inorganic porous materials is MOFs, which recently are utilized as efficient drug delivery systems. Since MOFs firs were discovered in 1989, [2] they exhibited versatile properties in a broad range of applications for their great surface area and simply access to the pores. Some of these applications are separation, catalysis, and sensing, and recently pharmaceutical applications. Recently, nano drug delivery systems pave the way to attain remarkable goals including transetiosis of the drug agents within the cell membranes, the intracellular delivery of encapsulated material in a targeted way and also theranostics. [3] Currently, a branch of nanoMOFs which are based on poriferous iron (III) polycarboxylates (Fe-nanoMOFs) has been developed as an excellent category of non-toxic and biodegradable materials for drug delivery applications. The ability to encapsulation of wide range of drug molecules in an incomparable amount (20-70 wt%) is one of the prominent features of these MOFs. [4–8] Despite these features, achieving targeted drug delivery systems is one of the most challenging issues. In this paper, we report the synthesis of coated-MIL-100(Fe) from octahedral iron (III), BTC organic linker and sodium alginate as a coating; using autoclave assisted hydrothermal technique.

Metformin (Scheme 1), as a drug to the treatment of type II diabetes, [9,10] has been utilized here as a model drug. Subsequently, in order to protect this MOF in simulated gastric environments and to attain a targeted release in the simulated intestinal medium, sodium alginate as a biocompatible and pH-sensitive coating was wielded which has a good track record in biomedical applications. [11]



Scheme 1. Structure of Metformin.

2. Experimental

2.1. **Materials and characterization**

In this work, all chemical reagents were purchased from Merck and Sigma-Aldrich (of analytical grade) and used without further purification. Fourier transform infrared (FT-IR) spectroscopy was carried out to ensure the product attainment and the spectrum was recorded on Nicolet Magna-550 spectrometer in KBr pellet. X-ray diffraction (XRD) patterns were conducted on a Philips X'pert pro diffractometer using Ni-filtered Cu Kα radiation. The thermogravimetric diagrams were obtained with a BAHR STA 504 using a heating rate of 5 ^{o}C min^{-1} from 50 ^{o}C to 800 ^{o}C in an air flow. UV–vis spectroscopy analysis using a Shimadzu UV-vis scanning spectrometer was carried out to monitor the drug release from the MOF.

3. Result and discussion

3.1 Synthesis and Characterization of the MOF and drug-loaded MOF

A mixture of iron trichloride and 1,3,5 benzene tricarboxylic acid (BTC) in the ratio of 2.5:1 were placed in a teflon-lined autoclave, after 7 hour mixture turned to an orange suspension which signified the MIL-100(Fe) formation. In order to the synthesis of drug-loaded MOF the as-synthesized MOF particles were swallowed in an aqueous solution of metformin 400mg/L for 24 h under magnetic stirring at room temperature then the solution was centrifuged 10 min, 10000 × g. The characterization of the frameworks was investigated by FT-IR spectroscopy. The FT-IR spectra of MIL-100(Fe) and metformin loaded-MIL-100(Fe) are shown in Figure 1. The relevant vibrational bands around 1448, 1386, 760, and 710 cm^{-1} which are characteristic bands of the MIL-100(Fe) confirmed the framework formation (Figure 1. top),[12] while in the FT-IR spectrum of metformin loaded-MIL-100(Fe) in addition to the peaks that are related to the framework, drug relevant peaks are observed (Figure 1. bottom).

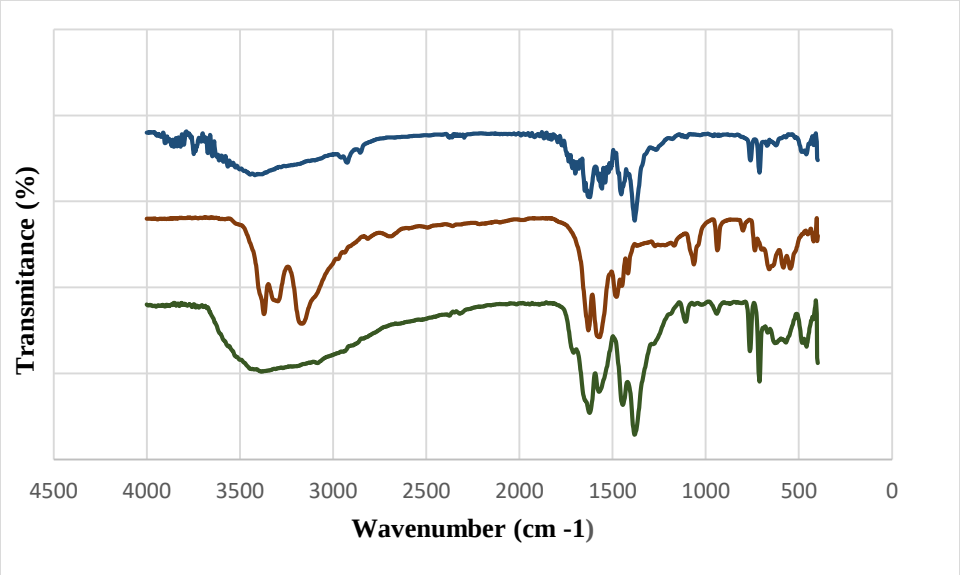


Figure 1. FTIR spectra of MIL-100(Fe), Metformin (middle) Metformin-loaded MIL-100(Fe)

3.2. Synthesis and Characterization of the alginate-coated MOF

The metformin loaded-MIL-100(Fe) particles were immersed in an aqueous solution of sodium alginate in the ratio of 1:0.5, respectively for 2.5 h under magnetic stirring at room temperature after that the solution was centrifuged 10 min, 10000 × g. FT-IR, TGA, and X-ray analysis were used to investigate the effect of coating on particles characteristic and crystallinity. The FT-IR spectra of MIL-100(Fe) and alginate-coated MIL-100(Fe) are shown in Figure 2. In the FT-IR spectra of the alginate-coated MIL-100(Fe), in addition to the appearance of typical MIL-100(Fe) peaks, the bands related to alginate vibrations are apparent as well. Although many of the peaks have been overlapped, the middle weak peaks at 1076 and 1150 cm^{-1} are related to alginate. Thermogravimetric analysis (TGA) has been done in order to evaluate the thermal behavior of MIL-100(Fe) and alginate-coated MIL-100(Fe) (Figure 3). The top curve belongs to MIL-100(Fe), which is completely compatible with that reported in the literature. [12] The TGA curve of alginate-coated MIL-100(Fe) (bottom) exhibits a similar thermal behavior, although, with additional loss of the weight 7 wt. %) is related to the presence of alginate on the framework. As

shown in Figure 4, The PXRD analysis demonstrates that the crystallinity structure of the MOF particles did not affect by coating.

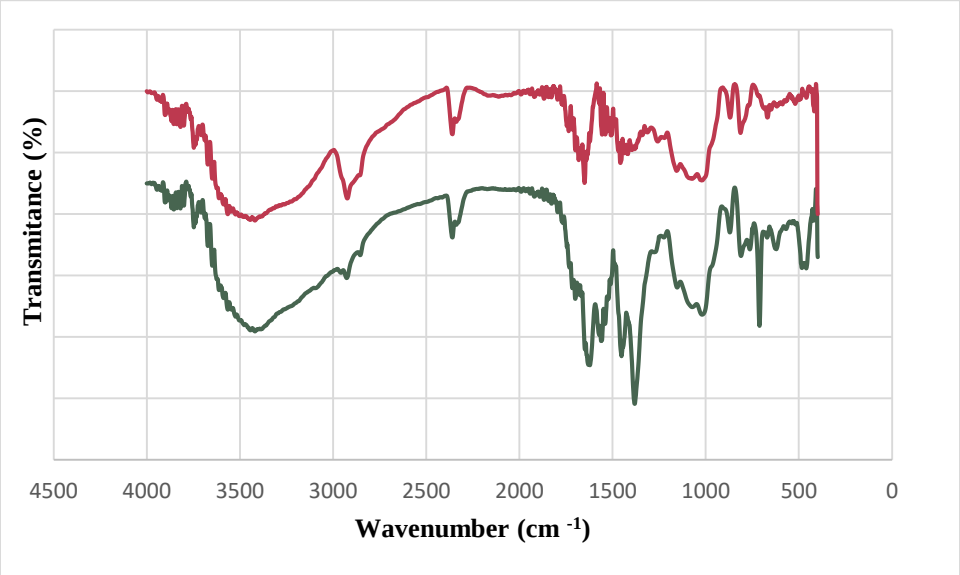


Figure 2. FT-IR spectra of MIL-100 (Fe) (top), Alginate- Coated MOF (bottom).

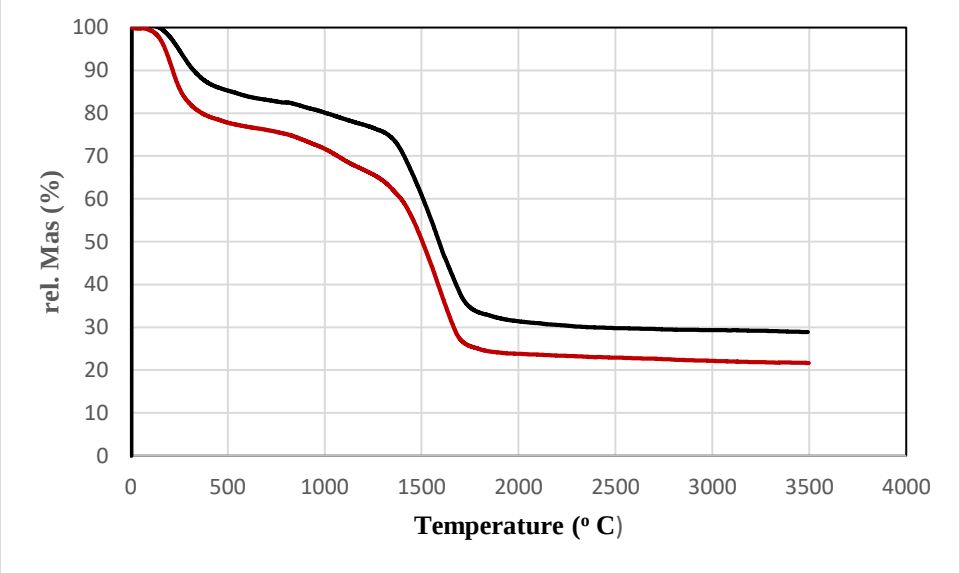


Figure 3. TGA curve of the MIL-100 (Fe) (top) and Alginate-coated MOF (bottom)

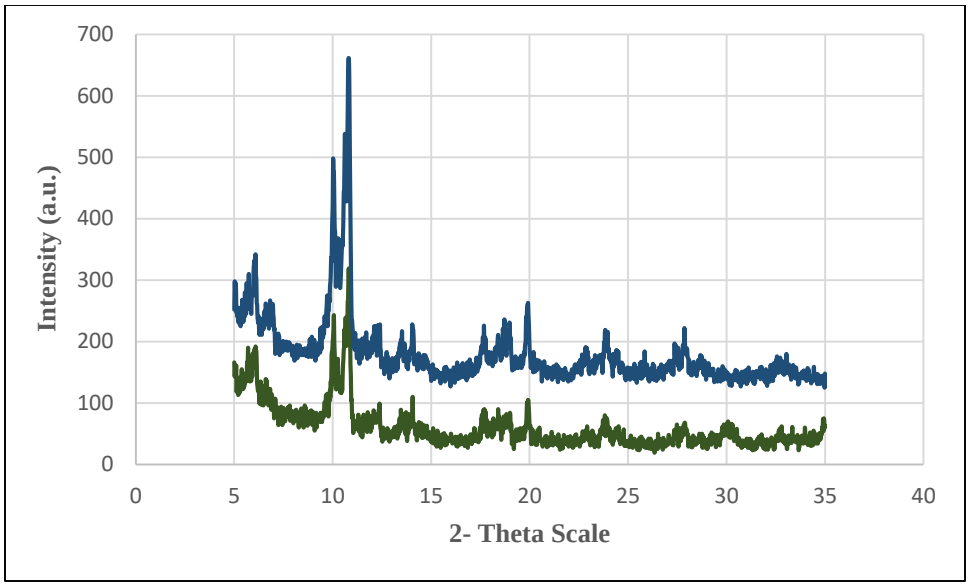


Figure 4. Powder XRD patterns of MIL-100(Fe) (top) and Alginate-Coated MIL-100(Fe) (bottom).

3.3. Drug release

To examine the release procedure, a certain amount of drug-loaded MIL-100(Fe) was immerged in the buffered saline (PBS) under magnetic stirring at 37 ° C in pH 8. In order to monitor the release behavior slight amount of the solution was picked up in different times and were analyzed by UV-Vis spectroscopy. The UV-Vis curve showed that drug release from the framework occurred in a selective and controlled manner in simulated intestinal medium (Figure 2). Controversy, in acidic pH the drug release was slightly.

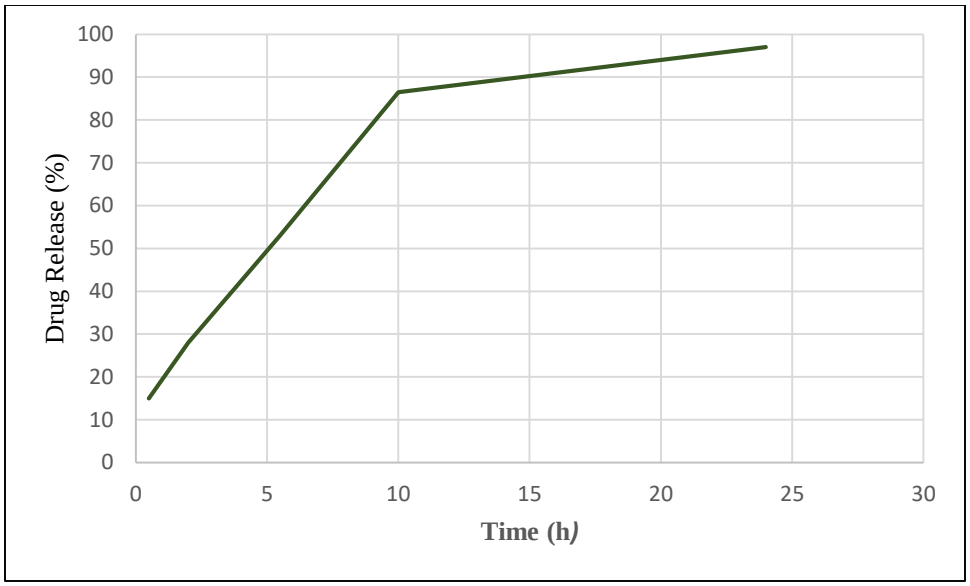


Figure 5. Metformin release from Alginate-Coated MIL-100(Fe) in PBS pH 8 at 37°C.

.

4. Conclusion

In summary, we demonstrated successful encapsulation of metformin inside alginate-coated MIL-100(Fe) frameworks via a green synthesis process avoiding any kind of detrimental solvents. The efficiency of drug encapsulation is 89% which is highly considerable among drug delivery systems. The pH-sensitive characteristic of alginate as the coating can be utilized to trigger targeted drug release in high pH media as in small intestine environment which it leads to efficient absorption of the drug.

Acknowledgments

The authors gratefully acknowledge the partial support from the Research Council of the Iran University of Science and Technology.

References

1. Faraji, A. & Wipf, P. Nanoparticles in cellular drug delivery. *Bioorganic Med. Chem.* **17**, 2950–2962 (2009).

2. Hoskins, B. F. & Robson, R. Infinite polymeric frameworks consisting of three dimensionally linked rod-like segments. *J. Am. Chem. Soc.* **111**, 5962–5964 (1989).

3. Horcajada, P. *et al.* Porous metal–organic-framework nanoscale carriers as a potential platform for drug delivery and imaging. *Nat. Mater.* **9**, 172–178 (2010).

4. Horcajada, P., Serre, C. & Vallet Regi, M. Metal–organic frameworks as efficient materials for drug delivery. *Angew. Chemie Int. Ed.* **45**, 5974–5978 (2006).

5. Agostoni, V. *et al.* Towards an Improved anti-HIV Activity of NRTI via Metal-Organic Frameworks Nanoparticles. *Adv. Healthc. Mater.* **2**, 1630–1637 (2013).

6. Chalati, T. *et al.* Porous metal organic framework nanoparticles to address the challenges related to busulfan encapsulation. *Nanomedicine* **6**, 1683–1695 (2011).

7. Horcajada, P. *et al.* Flexible porous metal-organic frameworks for a controlled drug delivery. *J. Am. Chem. Soc.* **130**, 6774–6780 (2008).

8. Cunha, D. *et al.* Rationale of drug encapsulation and release from biocompatible porous metal–organic frameworks. *Chem. Mater.* **25**, 2767–2776 (2013).

9. Cheng, A. Y. Y. & Fantus, I. G. Oral antihyperglycemic therapy for type 2 diabetes mellitus. *Can. Med. Assoc. J.* **172**, 213–226 (2005).

10. Charbonnel, B., Karasik, A., Liu, J., Wu, M. & Meininger, G. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. *Diabetes Care* **29**, 2638–2643 (2006).

11. Tønnesen, H. & Karlsen, J. Alginate in drug delivery systems. *Drug Dev. Ind. Pharm.* **28**, 621–630 (2002).

12. Tan, F. *et al.* Facile synthesis of size-controlled MIL-100 (Fe) with excellent adsorption capacity for methylene blue. *Chem. Eng. J.* **281**, 360–367 (2015).