Metal-Organic Frameworks as an Appropriate Platform for Controlled Drug Release

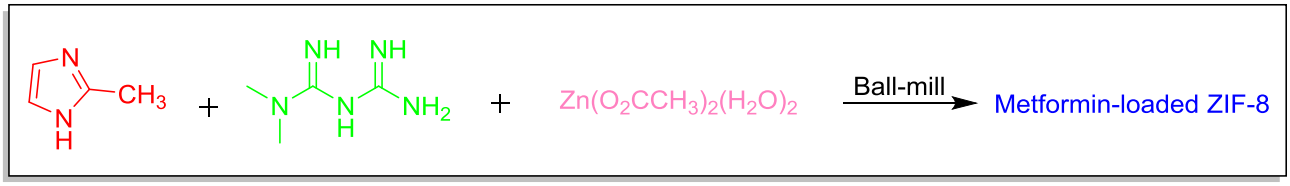
Tahereh Azizi Vahed, Mohammad Reza Naimi-Jamal*, Leila Panahi
Department of Chemistry, Research Laboratory of Green Organic Synthesis & Polymers, Iran University of Science and Technology, Tehran ١٦٨٤٦١٣١١٤, Iran
Email: naimi@iust.ac.ir

Abstract
Herein we used MOFs as a platform for controlled drug release and reported a technique, which pharmaceutical agents are encapsulated in a zinc zeolitic imidazolate framework (ZIF-٨). In this work, metformin, an oral antihyperglycemic agent for the treatment of type II diabetes trapped inside the ZIF-٨ pores through a mechanochemical ball-milling technique. Due to having regular porosity and zinc ions, ZIF-٨ could help to better absorption of metformin. The synthesis of the MOF and the encapsulating process of the drug were performed by using a convenient solvent-free one pot technique. It was shown that with this approach, metformin is released in the stomach via a controlled manner over a longer time that leads to increases of metformin bioavailability.

Keywords: ZIF-٨, Metformin, drug delivery, controlled release

Introduction

Metal-organic frameworks are a class of porous materials which are synthesized trough the self-assembly of metal ions and organic linkers. These particles have high pore volume and surface area; hence they are highly appropriate for the use as catalysts, sensors, absorbent and most recently in medicine. [١-٦] Recent studies illustrated that the MOFs can be promising platforms to entrap and gradual release of drugs or biomolecules. The first use of the MOFs as a drug delivery platform was carried out by Ferey et al in 2004 [7] and then other studies proved that these particles have a high payload efficiently (٢٠-٧٠٪) [٨] to encapsulate the drug molecules. Among these MOFs, ZIF-٨ with a pH-sensitive property, suitable shape and size is a non-toxic framework which has a good track record in using as drug delivery systems (DDS).[٩,١٠] Herein we utilized ZIF-٨ nanoparticles to encapsulate and controlled release of metformin. This method is based on a solvent free and one-pot mechanochemical reaction that the drug-loaded nanoparticles were synthesized via the ball milling a mixture of reactants such as zinc ion source (zinc acetate), ٢-Methylimidazole (an organic linker) and metformin as a model drug (Scheme ١).



Scheme ١. Synthesis of metformin-loaded ZIF-٨

Experimental

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-٥٥٠ spectrometer in KBr pellet. UV–vis spectroscopy analysis using a Shimadzu UV-vis scanning spectrometer was carried out to monitor the drug release from the MOF.

Synthesis of drug-loaded MOFs

A mixture of zinc acetate, ٢-Methylimidazole and metformin in the ratio of ١:٢:٠.٥ were placed in the ball milling case, after ١ hour mixture turned to milky dough which signified the MOF forming. Relevant peaks in the IR spectrum confirmed formation of the drug-loaded MOF which in addition to the peaks that are related to the framework, drug relevant peaks were observed in the spectrum (Figure ١).

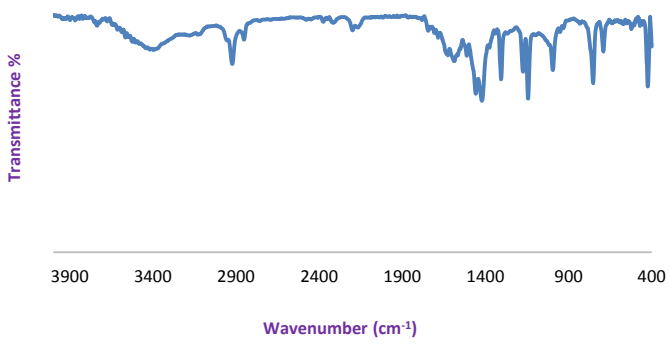


Figure ١. IR spectrum of Met-loaded ZIF-٨

Result and discussion

To investigate the release procedure, a certain amount of drug-loaded ZIF-٨ was incubate in the buffered saline (PBS) under magnetic stirring at ٣٧ ° C and in different times a small amount of the solution was analyzed by UV-vis spectroscopy. We investigated the released drug concentration in different time and the curve showed controlled release of the drug from the framework (Figure ٢).

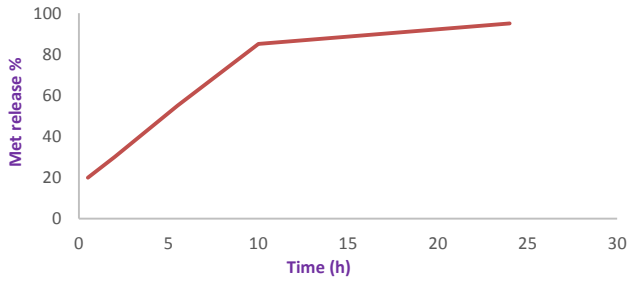


Figure ٢. Metformin release from ZIF-٨ in PBS pH ٧.٤ at ٣٧°C.

Conclusion

In summary, we have achieved an appropriate platform to increase the bioavailability of metformin, a high challenging drug. This process was done through a green solvent free, one-pot and short time reaction that drug molecules were encapsulated in ZIF-٨ particles, coincided with the nanoparticles synthesis.

Acknowledgements

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

References:

1. Zhao, D., et al., *Tuning the topology and functionality of metal– organic frameworks by ligand design.* Accounts of chemical research, 2010. 44(2): p. 123-133.
2. Corma, A., H. García, and F. Llabrés i Xamena, *Engineering metal organic frameworks for heterogeneous catalysis.* Chemical Reviews, 2010. 110(8): p. 4606-4655.
3. Li, J.-R., R.J. Kuppler, and H.-C. Zhou, *Selective gas adsorption and separation in metal–organic frameworks.* Chemical Society Reviews, 2009. 38(5): p. 1477-1504.
4. Keskin, S. and S. Kızılel, *Biomedical applications of metal organic frameworks.* Industrial & Engineering Chemistry Research, 2011. 50(4): p. 1799-1812.
5. Yang, X.L., et al., *A Multiresponsive Metal–Organic Framework: Direct Chemiluminescence, Photoluminescence, and Dual Tunable Sensing Applications.* Advanced Functional Materials, 2016. 26(3): p. 393-398.

6. Kaur, R., et al., *Recent advances in the photovoltaic applications of coordination polymers and metal organic frameworks.* Journal of Materials Chemistry A, 2016. 4(11): p. 3991-4002.
7. Férey, G., et al., *A hybrid solid with giant pores prepared by a combination of targeted chemistry, simulation, and powder diffraction.* Angewandte Chemie, 2004. 116(46): p. 6456-6461.
8. Agostoni, V., et al., *A "green" strategy to construct non-covalent, stable and bioactive coatings on porous MOF nanoparticles.* Scientific reports, 2015. 5.
9. Zhuang, J., et al., *Optimized metal–organic-framework nanospheres for drug delivery: evaluation of small-molecule encapsulation.* ACS nano, 2014. 8(3): p. 2812-2819.
10. Tian, Z., X. Yao, and Y. Zhu, *Simple synthesis of multifunctional zeolitic imidazolate frameworks-8/graphene oxide nanocrystals with controlled drug release and photothermal effect.* Microporous and Mesoporous Materials, 2017. 237: p. 160-167.