Research and Reviews: Drug Delivery

Synthesis and Characterization of Zeolitic Imidazolate Framework-8 Nanoparticles for Loading and Controlled Release of Cefazolin Drug

Lida Hassanzadeh, Aziz Babapoor*, Ali Nematollahzadeh

Department of Chemical Engineering, University of Mohaghegh Ardabili, Ardabil, Iran

Research Article

Received: 21-July-2022, Manuscript No. DD-22-64543;
Editor assigned: 27-July-2022, PreQC No. DD-22-64543(PQ);
Reviewed: 11-Aug-2022, QC No. DD-22-64543;
Revised: 18-Aug-2022, Manuscript No. DD-22-64543(R);
Published: 25-Aug-2022, DOI : 10.4172/resrevdrugdeliv.6.3.003
***For Correspondence:**
Aziz Babapoor, Department of Chemical Engineering, University of Mohaghegh Ardabili, Ardabil, Iran
E-mail: babapoor@uma.ac.ir
Keywords: Zeolitic Imidazolate Framework-8; Nanoparticles; loading; Release; Cefazolin

ABSTRACT

In recent decades, due to the spread of various diseases that have endangered human health, as well as due to inefficiency and less effectiveness and side effects of existing drugs and treatments, special attention has been paid to new treatments. One of these methods is the use of drug carriers. To this end, in this study, the ZIF-8 NPs were synthesized. These nanoparticles were characterized by FT-IR, TGA, SEM, BET, Zeta Potential, and UV-visspectroscopy. After synthesis, cefazolin drug was loaded on these nanoparticles. The drug loading amount was 12.54%. Then drug release in phosphate buffer with pH=7.4 was investigated. The release rate was 82.61%, which is excellent. These outcomes demonstrated that ZIF-8 nanoparticles have good potential for the controlled release of cefazolin.

INTRODUCTION

There has been significant progress in the medicinal industry in the bygone few decades. With the greatening number of illnesses, different novel drugs and various drug delivery procedures have been found [1]. However, the remedial effect of drugs has to be reduced strongly due to their poor solvability, speedy release, short circulation, and nonselective bio dispensation [2]. Nanomedicine is significantly searching to better the effect of therapeutic factors. Drug delivery systems remarkably smoothed this way through the typical method for the encapsulation of medicinal agents, memorize them versus degradation and control the drug release process [3]. With progress in the field of nanomedicine [4]. Many nanoscale carriers have appeared over the past decade for drug delivery, cell, and tissue imaging [5]. Lately, nanoparticles with functionalized carbon family networks such as graphene, graphene oxide, carbon nanotubes, carbon dots, and fullerenes have demonstrated considerable promise for cancer targeting and drug delivery in special chemotherapy treatments [6,7]. The dimension and surface attributes of magnetic nanoparticles converted them suitable candidates for the manufacture of functional nanostructures. By modifying magnetic nanoparticles with biocompatible materials, products became closer one step to medical and pharmaceutical applications such as diagnostics and drug delivery systems [8]. Notwithstanding all the advantages of extending nanomaterials, there are yet some substantial subjects stayed that should be attended to avoid affecting living organisms in detrimental ways [9]. If wide tries are made for extending nanotechnology and its betterment, it is possible to make the world a safer place for living [10]. Lately, metal-organic frameworks (MOFs) have been extensively utilized as new drug carriers the cause of the tunable pore size, significant pore volume, great specific surface area, and very typical crystalline porous network specification [11,12]. Between the MOFs, Zeolitic Imidazolate Frameworks (ZIFs) have attracted very consideration, for their various applications for instance, gas storage, chemical separation, catalysis, sensing, and drug delivery, owing to their excellent porosity, rigid structure, high surface area, good biocompatibility, and particular chemical and thermal stabilities [13,14]. Between ZIFs, ZIF-8 was exclusively promising for the usage as a drug carrier because ZIF-8 was a biocompatible and nontoxic MOF made from metal zinc ions with an organic ligand 2-methylimidazole [15,16]. Zeolitic imidazolate framework-8 can be utilized to build pH-responsive drug delivery systems [11]. Yang, et al. synthesized folate-targeted zinc-based nano MOFs through post-synthetic modification and investigated their efficiency as a targeted drug carrier *in vitro*. In the drug loading examination, the MOFs functionalized with folate rapidly adsorbed up to 24 wt% 5-fluorouracil. The percentage of drug release was 49% at 24 h [17]. Wang, et al. showed two Zn (II)-based MOFs with extra negative charges that have been utilized as drug carriers of 5-fluorouracil. The loading of the 5-fluorouracil drug into MOFs was around 0.22 g/g and 0.38 g/g [18]. Mocniak, et al. illustrate methods for the loading cisplatin drug, and a Pt (IV) cisplatin pro drug into two MOF, Ui066 and Ui066- NH_2. The EDX analysis shows that the cisplatin loading is 4.7 wt% in Ui066 and 4.9 wt% in Ui066-NH_2. Ui066 releases 22.73 µg of cisplatin per mg of nanoparticle in the first 24 h, and Ui066-NH_2 releases 5.88 µg of cisplatin per mg of nanoparticle [19]. Vasconcelos, et al. investigated the loading of the doxorubicin into the ZIF-8. They showed that doxorubicin is loaded into ZIF-8 to amount 0.049 g/g^{-1}. The percentage of doxorubicin release was obtained 66% during 30 days [20]. Chowdhuri, et al. have successfully designed and built core-shell up conversion nanoscale MOFs. The doxorubicin drug is loaded into NMOFs to amount 1.42 g/g^{-1}, and showed pH-responsive drug release [21]. Nadizadeh, et al. extended a mechanically new *in situ* drug loading method into Cu-NMOFs. Ibuprofen-loaded NMOFs were synthesized *via* ball-milling at room temperature in 2 h. The percentage of loading for ibuprofen in two MOFs was characterized by about 50.54% and 50.27%. Entire of the loaded drug was released in 1 day [22].

Although much research has been done on the controlled release of drugs, due to the importance and practicality of this issue in treating various diseases, more research is still needed in this area. Therefore, in this study, we examined the effect of zeta potential of nanoparticles on drug loading amount. These cases have been less studied before. In this study, ZIF-8 nanoparticles as carriers for loading and controlled release of cefazolin were investigated. The ZIF-8 NPs were synthesized in methanol solvent at room temperature. These nanoparticles were characterized by FT-IR, TGA, SEM, BET, Zeta Potential, and UV-visspectroscopy. After synthesis, cefazolin drug was loaded on these nanoparticles. The drug loading amount was 12.54%. Then drug release in phosphate buffer with pH=7.4 was investigated. The release rate was 82.61%, which is excellent. These outcomes demonstrated that ZIF-8 NPs have good potential for the controlled release of cefazolin.

MATERIALS AND METHODS

Synthesis of ZIF-8 nanoparticles

One solution was prepared by adding 0.1466 g of Zn $(NO_3)2.6H_2O$ to 10 ml of methanol and stirring for 20 min on the stirrer, and the second solution was prepared by adding 0.3244 g of 2-methylimidazole to 10 ml of methanol and stirred on the stirrer for 20 min, Zinc nitrate solution was then added to the 2-methylimidazole solution. The mixture was slightly milky, and then stirred for one hour the stirrer. Then Synthesis solution was centrifuged at 10,000 rpm for 10 min. The synthesized nanoparticles were washed twice with 5 ml of methanol, and finally, the synthesized zeolitic imidazolate framework-8 NPs were dried in an oven at 40 °C through 48 h [23].

Cefazolin loading method in ZIF-8 nanoparticles

Cefazolin solution was prepared with 5 ml of deionized water with pH=5 at a concentration of 100 ppm, and 0.01 g of nanoparticles were added to this solution. The solution was put in an ultrasonic bath for 2 min, and then the solution for 24 h was stirred on a stirrer, then the solution was centrifuged at 10,000 rpm for 10 min.

Method of investigating the release of cefazolin loaded in ZIF-8 nanoparticles

To investigate the release of cefazolin, ZIF-8 nanoparticles loaded with cefazolin were added to 20 ml of phosphate buffer with pH= 7.4. This solution was put inside the incubator at a speed of 120 rpm at a temperature of 37 °C. At certain intervals, the solution was removed from the incubator, and after centrifugation of the solution, the absorption amount of cefazolin released was obtained by a spectrophotometer.

RESULTS AND DISCUSSION

FT-IR analysis

The formation of ZIF-8 and cefazolin@ZIF-8 were approved by FT-IR analysis (Figure 1).The band in the spectral section of 3000-2500 cm-1could have pertained to N-H, C-H and O-H stretching vibrations of hydroxyl, methyl and amine groups on zeolitic imidazolate framework-8 nanoparticles [24]. In the FT-IR spectrum of ZIF-8 nanoparticles, the bands observed on 3135 and 2928 cm^{-1} corresponding to aromatic C-H stretching and aliphatic C-H stretching of imidazole, respectively [25,26].The peak at 1584 cm^{-1} can be allocated as the C=N stretch mode, particularly [27]. Whereas the strong and writhed bands at 1500-1350 cm^{-1} are related with the all loop stretching [28]. The bands in the spectral area of 1350–900 cm^{-1} are for the in-plane bending of the loop, while those under 800 cm^{-1} are allocated as out-of-plane bending [29]. The peak is seen in 1382 cm^{-1} corresponds to the all loop stretching. The peaks are seen in 690 and 760 cm^{-1} were related to aromatic sp2 C-H bending [1]. The absorption band at 420 cm^{-1} was related to the Zn-N stretching [30]. Evaluating the spectra obtained for the cefazolin@ZIF-8 with ZIF-8, it was

recognized that the spectra for the two samples demonstrated similarities very much. However, in the sample of cefazolin@ZIF-8, the sharpness and intensity of the peaks were incremented (Figure 1) [1].

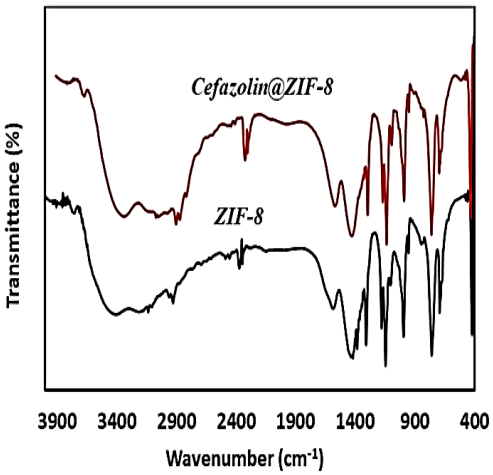

Figure 1. FTIR spectra of ZIF-8 and cefazolin@ZIF-8.

Thermal analysis

To investigate the mass changes in the ZIF-8 NPs and cefazolin@ZIF-8 by applying heat, a TGA analysis was performed, and the results of this analysis are shown in Figure 2. According to the ZIF-8 TGA curve, the curve consists of two parts. In the first part, which is up to about 278.3°C, a minimaldecrease in mass of 7.25 % occurred. It turns out that this is the stage of loss of sample moisture and the disappearance of soluble methanol molecules from cavities and other components of the nanoparticle surface [31]. In the second part of the curve, which is up to about 700.8°C, the mass decreased by 69.70%, which is related to the destruction of the organic molecules of 2-methylimidazole [32]. As the TGA curve of amoxicillin @ZIF-8 is very similar to that of ZIF-8, it shows that the thermal stability of ZIF-8 is not affected by the entry of drug molecules (Figure 2) [1].

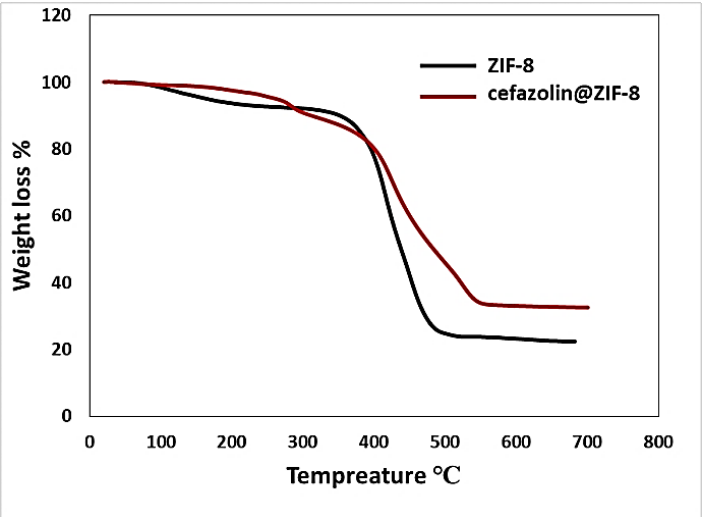

Figure 2. TGA curves of the ZIF-8 and cefazolin@ZIF-8 NPs. Note: (—) ZIF-8; (—) Cefazolin@ZIF-8

Surface morphology

SEM analysis was performed to evaluate the morphology of the surface and size of the ZIF-8 nanoparticles and cefazolin@ZIF-8. Based on these images, it is observed that the particle size is below 100 nm. The SEM images of ZIF-8 and cefazolin@ZIF-8 (Figure 3A and 3B) show the relative particle size 40 nm and 54 nm, respectively. Therefore, it is observed that with the adsorption of cefazolin in nanoparticles, the size of nanoparticles has increased.

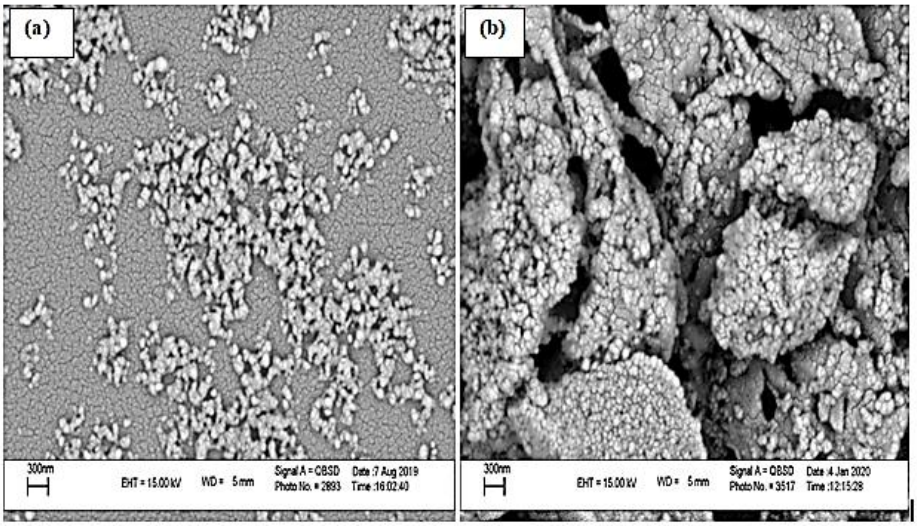

Figure 3. SEM analysis. A. SEM image of ZIF-8 NPs; B. SEM image of cefazolin@ZIF-8 NPs.

BET analysis

BET analyses were made to specify the porosity and surface area of cefazolin@ZIF-8 and ZIF-8. Nitrogen adsorption-desorption isotherms of ZIF-8 NPs and cefazolin@ZIF-8 NPs and pore size distribution are shown in Figures 4 and 5.The decrease in pore volume and BET surface area of cefazolin@ZIF-8 (0.3119 $cm^3\ g^{-1}$/663.93 $m^2\ g^{-1}$), as compared to ZIF-8 (0.6687 $cm^3\ g^{-1}$/1437.5 $m^2\ g^{-1}$) confirmed the loading of cefazolinin ZIF-8 nanoparticles (Figures 4 and 5).

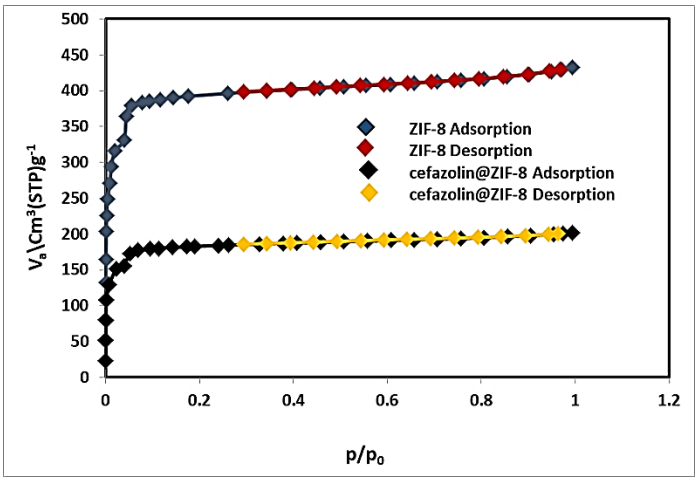

Figure 4. Nitrogen adsorption-desorption isotherms of ZIF-8 NPs and cefazolin@ZIF-8 NPs. Note: (—◆—) ZIF-8 Adsorption; (—◆—) ZIF-8 Desorption; (—◆—) Cefazolin@ZIF-8 Adsorption; (—◆—) Cefazolin@ZIF-8 Desorption

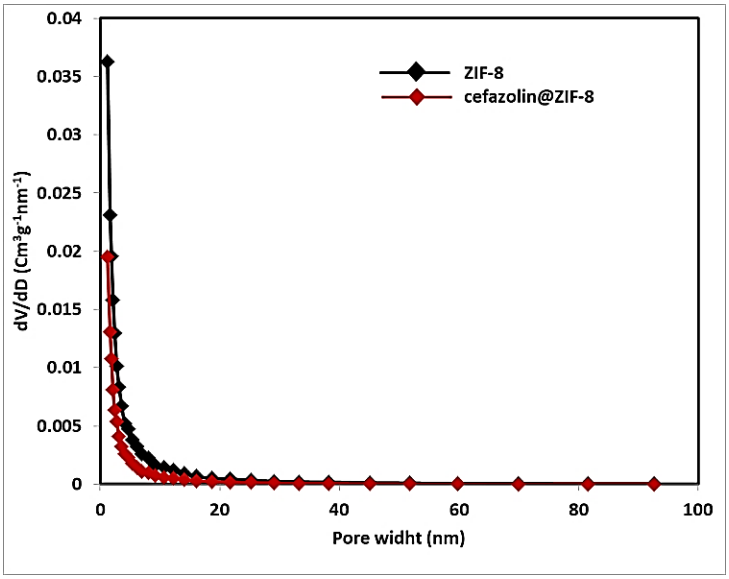

Figure 5. Pore size distribution curves of ZIF-8 NPs and cefazolin@ZIF-8 NPs. Note: (—◆—) ZIF-8; (—◆—) Cefazolin@ZIF-8

Zeta potential analysis

In order to obtain the isoelectric point of the synthesized ZIF-8 NPs, zeta potential analysis was taken from these nanoparticles (Figure 6). To obtain this analysis, up to 6 solutions of synthesized nanoparticles were prepared in phosphate buffers with pH 2.5, 3.5, 5, 7, 9, and 10. The zeta potential of these six solutions was measured.

Investigation of the effect of zeta potential on drug loading

According to the results obtained from the zeta potential analysis of nanoparticles, the isoelectric point of nanoparticles is between pH 2.5 and 3.5. On the other hand, pKa of the drug cefazolin is 3.6. So these two values are very close to each other. Hence, the surface charge of the nanoparticles and the drug is the same, and this reduces the drug loading. However, considering these conditions, the amount of drug loading obtained is reasonable and good (Figure 6).

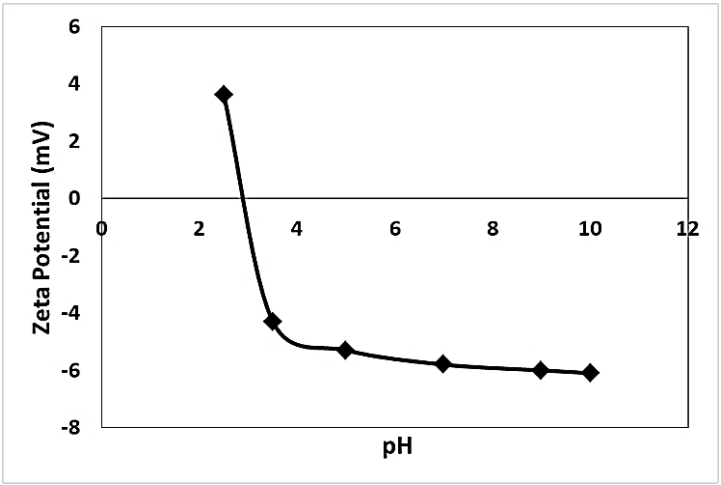

Figure 6. Zeta potential curve of ZIF-8 NPs.

Drug release study

Using the absorption data obtained from the spectrophotometer, the cefazolin drug's release curve was obtained in phosphate buffer with a pH=7.4, as shown in Figure 7. The drug loading percentage is 12.54%, which indicates that the loading rate of cefazolin in nanoparticles is excellent. The total concentration of the released cefazolin drug is 10.36 ppm, which is released within six h. Of the 12.54 ppm loaded drug, 10.36 ppm has been released. In other words, 82.61% of the loaded cefazolin drug has been released. Therefore, it is observed that ZIF-8 nanoparticles showed an excellent loading, and release rate for cefazolin (Figure 7).

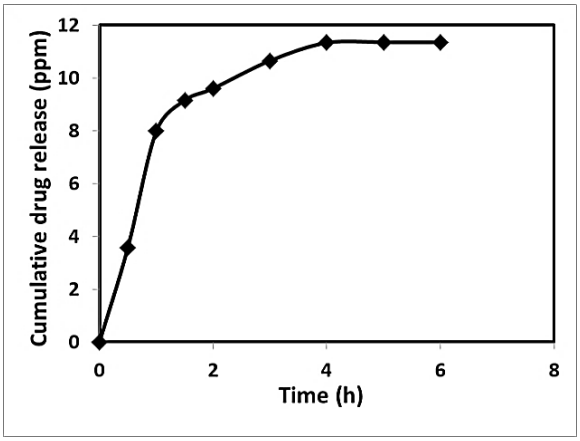

Figure 7. Cefazolin release profile from cefazolin@ZIF-8 in a phosphate buffer solution with a pH=7.4.

Investigation of drug release kinetics models

In this section, to investigate the release kinetics of cefazolin from ZIF-8 nanoparticles, zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell models were investigated. The data obtained for drug release were fitted with these models. The results of these fits are given in Table 1. According to these results, it is observed that the correlation coefficient (R^2) of the fit of these models is higher for the first-order model than other models, so the drug release kinetics among these five models is closer to the first-order model (Table 1) [33].

Table 1. Results of fitting of cefazolin release kinetic models.

R^2	Parameter	Model
0.6413	K0=4.4186	Zero order
0.9872	K1=11.4171	First order
0.8287	KH=5.6340	Higuchi
0.9294	KKP=7.22 n= 0.30	Korsmeyer-Peppas
0.5677	KHC=1.7387	Hixson-Crowell

CONCLUSION

In recent decades, on the one hand, due to the occurrence of various diseases, which have endangered human health, and on the other hand, the side effects of existing drugs, much attention has been paid to the issue of drug carriers and controlled release of drugs. In this study, the loading and controlled releases of cefazolin drug by ZIF-8 nanoparticles were investigated. ZIF-8 nanoparticles were synthesized at room temperature and in a methanol solvent. Cefazolin was successfully loaded into ZIF-8 nanoparticles after synthesis nanoparticles. Therefore, cefazolin@ZIF-8 nanoparticles were created. The ZIF-8 nanoparticles and cefazolin@ZIF-8 nanoparticles have been

characterized with diverse characterization tools. The loading of cefazolin drug was corroborated by diverse analyses of FTIR, BET, and so on. Thermal analysis showed that, loading of cefazolin into ZIF-8 did not affect its thermal stability. The percentage of cefazolin loading in ZIF-8 nanoparticles was 12.54%, which is a high value in drug loading. The percentage of cefazolin release in phosphate buffer with pH=7.4, during six h, was obtained 82.61%. The percentage of drug release is high and excellent. The outcomes of this study show that ZIF-8 nanoparticles demonstrated excellent behavior in loading and releasing cefazolin and, therefore, can be very promising carriers in this case.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The authors accept ethics approval and consent to participate.

CONSENT FOR PUBLICATION

The authors allow consent for publication.

AVAILABILITY OF DATA AND MATERIALS

Data and materials are unavailable.

COMPETING INTERESTS

The authors declare that there is no conflict of interest.

FUNDING

No funding has been received for this article.

AUTHORS' CONTRIBUTIONS

All authors have given contributions to the manuscript.

ACKNOWLEDGEMENT

This work was supported by the University of Mohaghegh Ardabili.

REFERENCES

1. Kaur H, et al. Synthesis and characterization of Zif-8 nanoparticles for controlled release of 6-mercaptopurine drug. J Drug Deliv Sci Technol. 2017;41:106-112.
2. Jiang K, et al. Thermal stimuli-triggered drug release from a biocompatibie porous metal-organic framework. Chem Eur J. 2017;23:1-8.
3. Azizi Vahed T, et al. Alginate-coated ZIF-8 metal-organic framework as a green and bioactive platform for controlled drug release. J Drug Deliv Sci Technol. 2018;49:570-576.
4. Mousavi S, et al. Graphene Nano-ribbon based high potential and efficiency for DNA, Cancer therapy and drug delivery applications. Drug Metab Rev. 2019;51:91-104.
5. Jia F, et al. Multifunctional nanoparticless for targeted delivery of immune activating and cancer therapeutic agents. J Control Release. 2013;172:1020-1034.
6. Mousavi S, et al. Applications of graphene oxide in case of nanomedicines and nanocarriers for biomolecules: review study. Drug Metab Rev. 2019;51:12-41.
7. Mousavi S, et al. Development of hydrophobic reduced graphene oxide as a new efficient approach for photochemotherapy. RSC Adv. 2020;10:12851-12863.
8. Mohajeri Avval Zh, et al. Introduction of magnetic and supermagnetic nanoparticles in new approach of targeting drug delivery and cancer therapy application. Drug Metab Rev. 2019;52:157-184.

9. Mousavi SM, et al. Green synthesis of silver nanoparticles toward bio and medical applications: review study, Artificial Cells. Artif Cells Nanomed Biotechnol. 2018;46:S855-S872.
10. Mousavi SM, et al. Nanosensors for chemical, biological and medical applications. Med Chem. 2018;8:205-217.
11. Lei Z, et al. 2019. Reactive Oxygen Species Synergistic pH/H_2O_2-Responsive Poly(L-lactic acid)-block-poly(sodium 4- styrenesulfonate)/Citrate- Fe(III)@ZIF-8 Hybrid Nanocomposites for Controlled Drug Release. ACS Appl Bio Mater. 2019;2:3648-3658.
12. Chen G, et al. Controlled synthesis of Fe_3O_4@ZIF-8 nanoparticles for drug delivery. Cryst Eng Comm. 2013;20:7486-7489.
13. Yang K, et al. A supramolecular hybrid material constructed from pillar[6]arenebased host-guest complexation and ZIF-8 for targeted drug delivery. Chem Comm. 2013;54:9817-9820.
14. Zheng C, et al. ZnO-DOX@ZIF-8 Core-Shell Nanoparticles for pH-Responsive Drug Delivery. ACS Biomater Sci Eng. 2017;3:2223-2229.
15. Zhang H, et al. Rational design of MOF nanocarrier-based Co-Delivery system of Doxorubicin Hydrochloride/Verapamil Hydrochloride for overcoming multidrug resistance with efficient targeted cancer therapy. ACS Appl Mater Interfaces. 2017;9:19687-19697.
16. Zhu W, et al. Facile preparation of succinylated-zein-ZIF-8 hybrid for enhanced stability and pH-responsive drug delivery. Chem Eng Sci. 2020;228:115981.
17. Yang B, et al. Post-synthetic modification nanoscale metal-organic frameworks for targeted drug delivery in cancer cells. Pharm Res. 2017;34:2440-2450.
18. Wang J, et al. A combined experimental and theoretical insight into the drug delivery of nanoporous metal-organic frameworks. RSC Advances. 2015;5:85606-85612.
19. Mocniak KA, et al. Incorporation of cisplatin into the metal–organic frameworks UiO66-NH_2 and UiO66-encapsulation *vs.* conjugation. RSC Advances. 2015;5:83648-83656.
20. Vasconcelos IB, et al. Cytotoxicity and slow release of the anti-cancer drug doxorubicin from ZIF-8. RSC Advances. 2012;2:9437-9442.
21. Chowdhuri AR, et al. Synthesis of multifunctional upconversion NMOFs for targeted antitumor drug delivery and imaging in triple negative breast cancer cells. Chem Eng J. 2017;319:200-211.
22. Nadizadeh Z, et al. Mechanochemical solvent-free *in situ* synthesis of drug-loaded {Cu_2(1,4-bdc)2(dabco)}n MOFs for controlled drug delivery. J Solid State Chem. 2017;259:35-42.
23. Cravillon J, et al. Rapid room-temperature synthesis and characterization of nanocrystals of a prototypical zeolitic imidazolate framework. J Am Chem Soc. 2019;21:1410-1412.
24. Jian M, et al. Adsorptive removal of arsenic from aqueous solution by zeoliticimidazolate framework-8 (ZIF-8) nanoparticles. Colloids Surf A: Physicochem Eng Asp. 2015;465: 67-76.
25. Nabipour H, et al. Synthesis and characterization of nanoscale zeolitic imidazolate frameworks with ciprofioxacin and their applications as antimicrobial agents. New J Chem 2019;41:7364-7370.
26. Tiwari A, et al. Curcumin encapsulated zeolitic imidazolate frameworks as stimuli responsive drug delivery system and their interaction with biomimetic environment. Sci Rep. 2017;7:12598.
27. He M, et al. Facile synthesis of zeolitic imidazolate framework-8 from a concentrated aqueous solution. Microporous Mesoporous Mater. 2014;184:55-60.
28. Ethiraj J, et al. H_2S interaction with HKUST-1 and ZIF-8 MOFs: A multitechnique study. Microporous

Mesoporous Mater. 2015;207:90-94.

29. Hu Y, et al. *In situ* high pressure study of ZIF-8 by FTIR spectroscopy. Chem Comm. 2011;47:12694-12696.
30. Liu J, et al. NiO-PTA supported on ZIF-8 as a highly effective catalyst for hydrocracking of Jatropha oil. Sci Rep. 2016;6:23667.
31. Yao J, et al. High-yield synthesis of zeoliticimidazolate frameworks from stoichiometric metal and ligand precursor aqueous solutions at room temperature. Cryst Eng Comm, 2013;15:3601-3606.
32. Schejn A, et al. Controlling ZIF-8 nano- and microcrystal formation and reactivity through zinc salt variations. Cryst Eng Comm. 2014;16:4493-4500.
33. Panotopoulos GP, et al. Mathematical modeling for pharmaco-kinetic and -dynamic predictions from controlled drug release nanosystems: A comparative parametric study. Scientifica. 2019.