17 Jan 2022

Combined Ibuprofen and Curcumin Delivery using Mg-MOF-74 as a Single Nanocarrier

Shane Lawson

Ali A. Rownaghi
Missouri University of Science and Technology, rownaghia@mst.edu

Fateme Rezaei
Missouri University of Science and Technology, rezaeif@mst.edu

Recommended Citation

S. Lawson et al., "Combined Ibuprofen and Curcumin Delivery using Mg-MOF-74 as a Single Nanocarrier," *ACS Applied Bio Materials*, vol. 5, no. 1, pp. 265 - 271, American Chemical Society, Jan 2022.
The definitive version is available at https://doi.org/10.1021/acsabm.1c01067

ACS APPLIED BIO MATERIALS

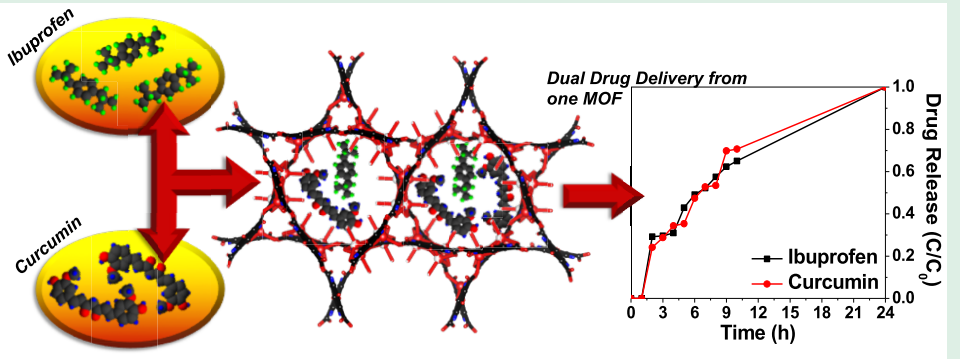
www.acsabm.org Article

Combined Ibuprofen and Curcumin Delivery Using Mg-MOF-74 as a Single Nanocarrier

Shane Lawson, Ali A. Rownaghi, and Fateme Rezaei*

Cite This: ACS Appl. Bio Mater. 2022, 5, 265−271 Read Online

ACCESS | Metrics & More | Article Recommendations



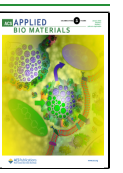
ABSTRACT: Metal−organic frameworks (MOFs) have been extensively used as drug delivery platforms because of their considerable textural properties and physiochemical tunability. However, most medicinal treatments often administer multiple therapeutic pharmaceuticals simultaneously and combined drug delivery over a single MOF carrier has not been extensively developed. As such, in this study we implemented Mg-MOF-74, which is known to have rapid pharmacokinetic properties, for the combined delivery of ibuprofen and curcumin to demonstrate the proof-of-concept for dual-drug delivery over this previously unexplored MOF. To this end, 30 wt % total drug loading of two drugs was impregnated at various ratios (25:5 ibuprofen−curcumin, 20:5 ibuprofen−curcumin, 15:15 ibuprofen−curcumin, 10:20 ibuprofen−curcumin, and 5:25 ibuprofen−curcumin), and the drug delivery performance of the materials was assessed from 0 to 24 h in phosphate-buffered saline (PBS) solution using high-performance liquid chromatography (HPLC). The experiments revealed that all five ratios of ibuprofen−curcumin loadings can effectively deliver both compounds; however, elevating the curcumin loading beyond 10 wt % decreases the drug loading efficiency for ibuprofen and can also inhibit ibuprofen release. Nevertheless, because Mg-MOF-74 was able to successfully deliver both compounds, this study serves as a promising proof-of-concept for dual-drug delivery from a single MOF carrier. In this regard, the work demonstrated herein expands the use of MOFs for drug delivery applications and can be used to supplement drug administration via orally ingested tablets.

KEYWORDS: *metal−organic framework (MOF), dual-drug delivery, pharmacokinetics, ibuprofen, curcumin*

1. INTRODUCTION

One of the most important areas in the medicinal sciences is the administration of therapeutic drug compounds, as this is a well-recognized and simple way to treat a host of ailments. Most often, pharmaceutical drugs are administered using orally swallowed tablet delivery systems; however, increasing the drug loading requires that larger tablets be used which can lead to difficulties swallowing. Besides, one of the biggest issues with tablet-based drug delivery is that digestion of the binder can lead to high concentrations of the drug being administered too quickly (e.g., burst effect), which can cause acute health problems such as nausea, liver failure, and pharmacological toxicity.[1] These complications are further amplified when multiple pharmaceutical agents are administered, such as in the case of neurological diseases where a cocktail of drugs is administered to both treat the underlying disease and lessen the severity of the symptoms.[2−4] For instance, simultaneously administering ibuprofen and curcumin has been shown to reduce neurological swelling in mice with Niemann-Pick disease to a greater degree than when each drug is administered individually. The reason for this is that combining both drugs targets different swelling mechanisms

Received: October 11, 2021
Accepted: December 14, 2021
Published: December 27, 2021



https://doi.org/10.1021/acsabm.1c01067
ACS Appl. Bio Mater. 2022, 5, 265−271

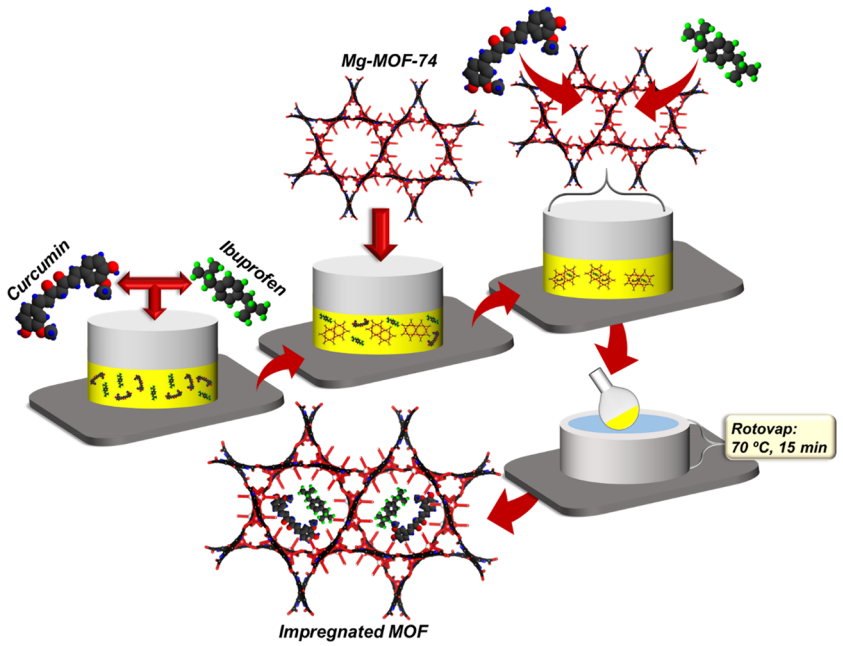


Figure 1. Schematic representation of dual-drug impregnation into a single Mg-MOF-74 carrier.

which leads to a synergetic effect upon administering the two pharmaceutical compounds in tandem.[3] Unfortunately, this synergism can be offset by simultaneous burst release of both drugs, which is considerably more dangerous than burst release of a single compound because of the greater load which is placed on the liver. In this regard, it is worth exploring novel drug delivery platforms to advance the area of dual-drug delivery.

In recent years, one alternative to conventional drug delivery has been to administer pharmaceutical compounds with nanoporous solid carriers, including zeolites, activated carbons, silica, and metal−organic frameworks (MOFs).[5−11] Among these materials, MOFs have attracted considerable interest over the past decade as attractive drug delivery platforms on the basis of their exceptionally high surface areas and pore volumes, tunable physiochemical properties, and wide degree of structural versatility with regard to their metal centers and organic ligands. Such properties not only allow for high concentrations of the drug to be considered but also can be used to maximize biocompatibility and enhance the pharmacokinetic release rate.[8,12,13] Nevertheless, most current studies which assess the performance of MOF materials for drug delivery have focused primarily on single-drug release, and very few studies have reported dual delivery over a MOF which has rapid pharmacokinetic release properties. Therefore, this area of research is worth exploring as it can potentially provide a novel pathway of unlocking the synergetic benefits of dual-drug delivery systems.

Motivated by the need to develop alternative pathways toward dual-drug delivery from a single-carrier approach, we embarked on a proof-of-concept study which utilizes Mg-MOF-74 for the combined delivery of ibuprofen and curcumin. This particular MOF was selected for this proof-of-concept investigation because our recent work indicated that the high solubility of Mg leads to rapid pharmacokinetics, whereas a combination of curcumin and ibuprofen was selected because of the aforementioned synergetic benefits that occur upon simultaneous administration of these pharmaceutical species.[3,12] The drug loading was optimized using different ratios of the two compounds, and the delivery performance was analyzed from 0 to 24 h in phosphate-buffered saline (PBS) solution. The drug delivery experiments revealed that increasing the curcumin loading leads to blockage of the active sites and prevents effective ibuprofen loading to a small degree; however, the MOF was still capable of delivering both drugs even with this limitation being present. As such, this study reports a proof-of-concept demonstration of dual-drug delivery from Mg-MOF-74, representing an important advancement in the rapid pharmacokinetic release of multiple drugs for synergetic therapeutic medicine.

2. EXPERIMENTAL SECTION

2.1. Materials. The following materials were purchased from Sigma-Aldrich and used to develop Mg-MOF-74 for combined ibuprofen and curcumin delivery: Na_2HPO_4 (98%), curcumin (99%), 2,5-dihydroxyterephtalic acid (98%), ibuprofen (99%), and $Mg(NO_3)_2{\cdot}6H_2O$ (99%). The following solvents and buffers were also used: ethanol (EtOH, ACS), methanol (MeOH, ACS), *N*,*N*-dimethylformamide (DMF, ACS), acetonitrile (ACN, HPLC), distilled water (HPLC), and phosphate-buffered saline (PBS, pH = 7.4). The carrier phase for HPLC was produced by dissolving Na_2HPO_4 in HPLC-grade water to make a 10 mM solution. All other reagents were used without modification.

2.2. Drug Impregnation. The Mg-MOF-74 was synthesized using its established solvothermal procedure.[14,15] It is also noted here that many of the physiochemical properties of Mg-MOF-74 can be found elsewhere.[16−18] The combined curcumin and ibuprofen loadings were impregnated onto Mg-MOF-74 using the wet-impregnation technique detailed in our earlier works (Figure 1).[8,12,18] Briefly, the desired amount of drug was dissolved in 20 mL of MeOH via sonication for 15 min. Both the ibuprofen and the curcumin were dissolved in the same MeOH solution in the desired ratio. Then, 0.1 g of Mg-MOF-74 was added to the flask, and the sample was mixed for 24 h under 400 rpm at 25 °C. The drug/MOF composite was recovered using rotary evaporation at 70 °C for 15 min. For all samples, the total drug loading was held at 30 wt % relative to the bare MOF (e.g., 0.03 g of drug per 0.1 g of MOF powder) because our previous study indicated that the drug release from Mg-MOF-74 becomes inhibited above that loading due to

https://doi.org/10.1021/acsabm.1c01067
ACS Appl. Bio Mater. 2022, 5, 265−271

oversaturation of the MOF textural properties by the impregnated pharmaceutical guests. However, the curcumin and ibuprofen concentrations were systematically adjusted to determine how the pharmacokinetic performance of the drug-loaded MOF changes with the ibuprofen/curcumin ratio. To this end, five samples were made: 25 wt % ibuprofen−5 wt % curcumin, 20 wt % ibuprofen−10 wt % curcumin, 15 wt % ibuprofen−15 wt % curcumin, 10 wt % ibuprofen−20 wt % curcumin, and 5 wt % ibuprofen−25 wt % curcumin. The weight ratios of the individual composites are summarized in Table 1.

Table 1. Component Masses Used for Impregnation of Dual-Drug Composites

sample	ibuprofen loading (g)	curcumin loading (g)	MOF loading (g)
25I:5C	0.025	0.005	0.1
20I:10C	0.020	0.010	0.1
15I:15C	0.015	0.015	0.1
10I:20C	0.010	0.020	0.1
5I:25C	0.005	0.025	0.1

2.3. Characterization. The textural properties of the bare MOF and drug-loaded samples were assessed using N_2 physisorption at −196 °C on a micromeritics 3Flex gas analyzer. Prior to analysis, the bare Mg-MOF-74 was degassed using the conditions from its synthesis procedures on a Micromeritics SmartVac Prep system.[14,15] The drug-loaded MOF samples were degassed at 100 °C for only 1 h to prevent evaporation of the drug loading. The sample surface areas and pore volumes were then calculated from the physisorption data by the Brunauer−Emmet−Teller (BET) and nonlocal density functional theory (NLDFT) methods, respectively. The surface functional groups of the drug-loaded MOF samples were assessed by Fourier transform infrared (FTIR) spectroscopy using a Nicolet iS50 FTIR equipped with an attenuated total reflectance (ATR) diamond. This measurement was used to confirm that ibuprofen and curcumin had both been successfully loaded. All other characterization methods for the bare Mg-MOF-74 used in this study (e.g., X-ray diffraction, and scanning electron microscopy) can be found in our recent work.[12]

2.4. Drug Delivery Experiments. The combined drug delivery performance of the five ibuprofen−curcumin samples was assessed in PBS solution from 0 to 24 h at 37.4 °C. Samples were collected every hour from 0 to 10 h and again at 24 h from the PBS solution to assess the combined drug delivery performance. It should be noted here that the drug concentration profiles plateaued after the first 12 h, with a near-zero change occurring after 24 h, so the experiments were terminated at the 24 h mark. Lastly, it should be noted that the single-drug delivery performance for Mg-MOF-74 can be found in our previous work.[12] The as-collected samples were then analyzed by HPLC in a C18 column using a method which has been reported for ibuprofen.[19] A full description of these experiments is located in our previous work.[8] After collecting the HPLC data, it was normalized with respect to one and the pharmacokinetic profiles were fitted using the Higuchi technique.[20]

3. RESULTS AND DISCUSSION

The N_2 physisorption isotherms and pore size distribution (PSD) profiles of the bare and drug-loaded samples are shown in Figure 2. The corresponding textural properties are displayed in Table 2. First looking at the adsorption isotherm for Mg-MOF-74 (Figure 2a), the bare MOF displayed a hybridized Type I−IV adsorption isotherm which is consistent with materials that contain both micro- and mesoporosity.[21] Indeed, this was corroborated by the NLDFT PSD profiles in

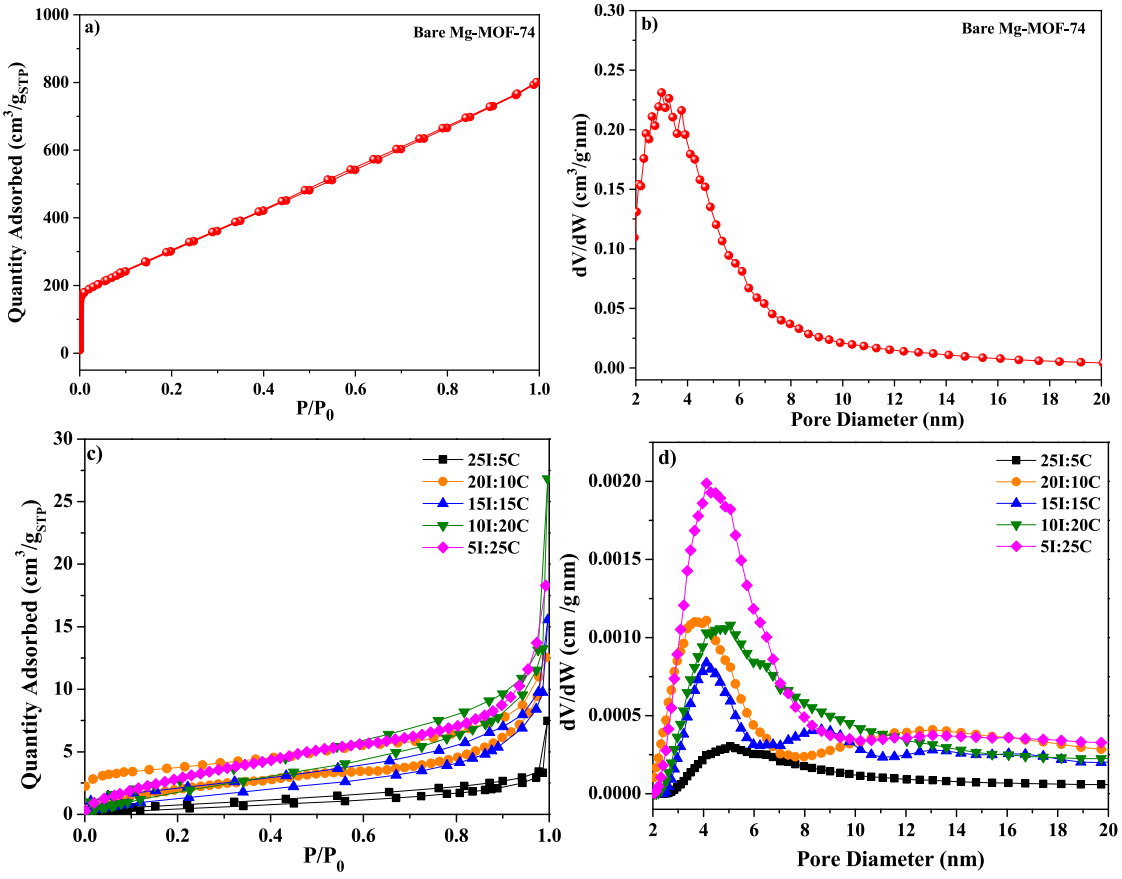


Figure 2. (Left) N_2 physisorption isotherms and (right) PSD profiles for (a and b) bare and (c and d) dual-drug-loaded Mg-MOF-74 samples.

https://doi.org/10.1021/acsabm.1c01067
ACS Appl. Bio Mater. 2022, 5, 265−271

Table 2. Textural Properties for Bare and Dual-Drug-Loaded Mg-MOF-74 Samples

sample	S_{BET} (m^2/g)	V_{micro} (cm^3/g)	V_{meso} (cm^3/g)	pore diameter (nm)
bare Mg-MOF-74	1180	0.45	0.71	2−10
25I:5C	10	0.00	0.01	
20I:10C	10	0.00	0.01	
15I:15C	10	0.00	0.01	
10I:20C	10	0.00	0.01	
5I:25C	20	0.00	0.02	

Figure 2b as the pristine Mg-MOF-74 displayed both micro- and mesopore structures. This physisorption behavior also agreed with the previous reports for Mg-MOF-74 synthesized by this method, as this MOF is known to have a hierarchal pore structure.[12,18] Meanwhile, the drug-loaded samples were essentially nonporous, as evidenced by their near-zero textural properties (Table 2) and the Type II (nonporous) physisorption isotherms (Figure 2c).[21] These effects indicated that dual-drug impregnation led to total filling of the pore windows, albeit with some slight retention of the mesopores as observed in Figure 2d. Notably, the mesopore volume seemed to decrease slightly with the ibuprofen loading, which was somewhat expected because ibuprofen is much smaller than curcumin, so it should fill the pore better. However, the differences in mesopore retention between the drug-loaded samples were small enough to lie within the instrument error, so a relationship between the ibuprofen/curcumin ratio and the retained textural properties could not be drawn with certainty. It could only be truly concluded that dual-drug impregnation completely saturates the MOF pores, which is a similar behavior to that which has been observed previously for single-drug-impregnated systems. For example, impregnating Mg-MOF-74 with a surface area of 1170 m^2/g, micropore volume of 0.45 cm^3/g, and mesopore volume of 0.71 cm^3/g with 30 wt % curcumin generated comparable textural properties to those observed here, namely, the MOF/curcumin composite only retained a surface area of 20 m^2/g, 0.00 cm^3/g micropore volume, and 0.03 cm^3/g mesopore volume after impregnation.[12] The similarities between the single- and dual-drug-impregnated systems indicated that the mechanism of the latter is similar to that of the former, effectively signifying that wet impregnation can be considered a facile means of loading multiple pharmaceutical species within a single MOF pore.

The FTIR spectra of the bare and drug-loaded MOFs are shown in Figure 3. First, it should be noted that the bare MOF displayed vibrational bands at 1580, 1405, 1240, 1190, 1120, 1026, 880, and 810 cm^{-1}, which are correlated to C═C/C═O conjugation, −OH, C−O, C−O, secondary alcohol C−O, anhydride, C═C, and C═C bonding, respectively, in the organic ligand.[22] After impregnating the ibuprofen and curcumin, the samples displayed new vibrational modes that were consistent with the FTIR spectra for both curcumin and ibuprofen. Regarding curcumin, new vibrational bands were observed at 1023, 2800, and 2900 cm^{-1}, which correspond to vibrational modes for C−O−C, C−H (methyl), and C−H (aryl), respectively, within the curcumin structure.[12,23,24] Regarding ibuprofen, it should be noted that many of the vibrational modes for this drug overlap with those of curcumin and Mg-MOF-74. For example, the characteristic peaks for ibuprofen are known to occur at 1720 and 2920 cm^{-1}, respectively, stemming from the carbonyl and hydroxyl groups

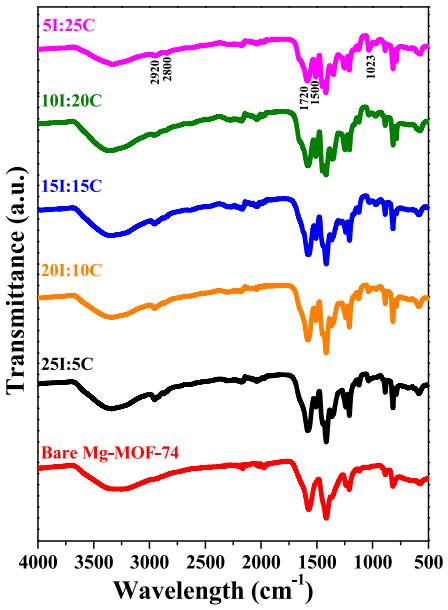


Figure 3. FTIR spectra of bare and dual-drug-loaded Mg-MOF-74.

of the drug.[25,26] Given that these functional groups are also present in curcumin, these peaks cannot be attributed to either drug. Nevertheless, ibuprofen also contributes a vibrational band at 1500 cm^{-1}, which was present in the drug-loaded samples but was absent in the bare MOF. This peak has been attributed to various modes of cyclic C═C stretching and arises from the aromatic ring within the ibuprofen structure.[25,26] Given that this peak was present alongside the characteristic vibrational modes for curcumin, it was concluded from Figure 3 that both drugs were loaded successfully.

The raw peak concentrations were collected from the drug delivery experiments for both ibuprofen and curcumin to show the effects of drug concentration on total species release. The peak area concentrations for ibuprofen are displayed in Figure 4a, whereas the peak area concentrations for curcumin are given in Figure 4b. Notably, the amount of ibuprofen delivered did not decrease in a perfect manner as would be expected from the theoretical drug loading. Specifically, the amount of ibuprofen delivered could be ranked from the HPLC data in the following order: 25I:5C > 20I:10C ≈ 10I:20C > 5I:25C > 15I:15C. This result indicated that ibuprofen impregnation was not always 100% efficient, essentially becoming random upon increasing the curcumin loading beyond 10 wt %. A similar degree of randomness was observed for the raw curcumin delivery, since the amount of curcumin delivered was found to descend in the following order: 5I:25C > 20I:10C > 15I:15C > 10I:20C > 25I:5C. On one hand, it can be argued that because the differences between some of these samples were very small they could have resulted from experimental error. This notion is supported by the fact that the 25I:5C sample released so much less curcumin compared to the 5I:25C sample as well as by the fact that the 10, 15, and 20 wt % curcumin samples all released similar amounts of the drug. In this regard, Figure 4 indicated that dual-drug delivery with Mg-MOF-74 is best achieved when one drug species is in much a higher concentration than the other, thereby allowing for precise control over the drug loading. Even with this limitation, Figure 4 still indicated that Mg-MOF-74 can be used for the combined delivery of two pharmaceutical compounds; thus, it

https://doi.org/10.1021/acsabm.1c01067
ACS Appl. Bio Mater. 2022, 5, 265−271

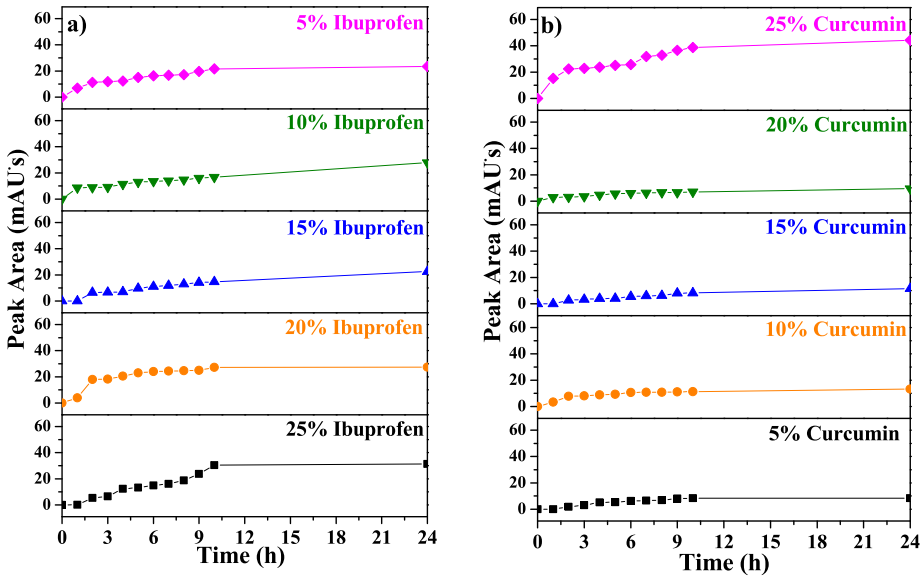


Figure 4. Raw peak area concentrations for (a) ibuprofen and (b) curcumin from dual-drug delivery experiments with Mg-MOF-74 in PBS solution over 24 h at 37.4 °C.

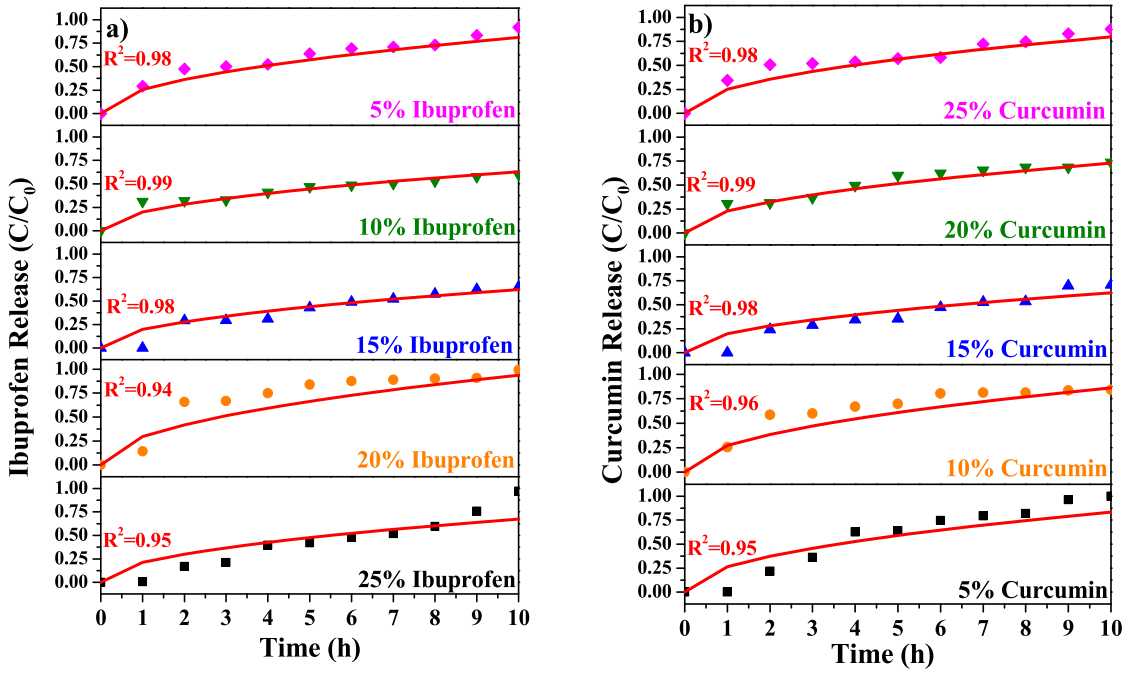


Figure 5. Normalized concentration profiles with Higuchi technique curve fittings for (a) ibuprofen and (b) curcumin from dual-drug delivery experiments with Mg-MOF-74 in PBS solution over 24 h at 37.4 °C.

represents a successful proof-of-concept for this new technique.

The normalized drug delivery concentrations for ibuprofen and curcumin were fitted with the Higuchi technique, as shown in Figure 5.[8,12] The corresponding diffusivity values are displayed in Table 3. First, it should be noted here that all R^2 values were greater than 0.9, signifying that the selected model appropriately represented the data set. In this regard, the curve fittings indicated that the mechanism of drug release was driven by diffusion of the pharmaceutical species from the MOF pores and not by layered release from the MOF surface.[27,28] It is also worth noting here that the diffusivity constants (Table 3) for both ibuprofen and curcumin were comparable to those we reported for just curcumin in our recent work, where the exceptional solubility of Mg^{2+} produced rapid diffusion of the drug from the MOF pore structure.[12]

Table 3. Calculated Diffusivity Constants from Dual-Drug Delivery Experiments for Ibuprofen and Curcumin from Mg-MOF-74

sample	ibuprofen diffusivity ($h^{1/2}$)	curcumin diffusivity ($h^{1/2}$)
25I:5C	0.21	0.26
20I:10C	0.30	0.27
15I:15C	0.20	0.20
10I:20C	0.19	0.23
5I:25C	0.26	0.25

https://doi.org/10.1021/acsabm.1c01067
ACS Appl. Bio Mater. 2022, 5, 265−271

Moreover, the release rate behaviors outlined in Figure 5 and the corresponding pharmacokinetic constants in Table 3 were competitive with single-drug delivery platforms. For example, Rojas et al. reported release rate constants for 25.5 wt % ibuprofen from MIL-100 (Fe) and UIO-66 of k = 0.21 and 0.11 $h^{-1/2}$,[29] respectively, whereas we previously reported a release rate of 30 wt % curcumin from Mg-MOF-74 of k = 0.30 $h^{-1/2}$.[12] Given that the release rate constants of the dual-drug-impregnated system were comparable to those which have previously been reported and are generally considered to be acceptable, impregnating ibuprofen and curcumin together onto Mg-MOF-74 was concluded to be an effective means of delivering both species in tandem at rapid pharmacokinetic rates. Furthermore, the retained pharmacokinetic rates in the dual-drug-impregnated system relative to those observed in single-drug systems indicated that impregnating multiple compounds does not significantly inhibit the release of either species from the pore window, which is a key concern when developing parallel drug release from a singular carrier. As such, it was concluded from Figure 5 that Mg-MOF-74 can successfully act as a platform for simultaneous delivery of two drugs, since it delivered both species without compromising the pharmacokinetic rate of delivery for either compound. Granted, the issue of control over the drug loading is one which still requires being addressed; however, this work is less difficult compared to developing a first-principle prototype of dual-drug delivery from a single carrier with rapid pharmacokinetic properties, since this issue can foreseeably be addressed by tuning the MOF synthesis to enlarge the pore window. In this regard, this study has demonstrated a successful proof-of-concept for this technology.

4. CONCLUSIONS

In this study, we demonstrated a first proof-of-concept for dual-drug delivery from Mg-MOF-74. Specifically, we impregnated different ratios of ibuprofen and curcumin and assessed the pharmacokinetic properties of the resulting MOF/drug composites. From the drug delivery experiments, it was determined that Mg-MOF-74 can effectively be implemented to deliver both drugs with controllable concentrations when the loading of one species is below ∼10 wt %; however, increasing the amount of the secondary species can reduce the efficiency of drug impregnation for the primary component. For example, the ibuprofen and curcumin loadings could be precisely controlled when a ratio of 25I:5C or 5I:25C was used; however, the amount of drug released was less tunable at drug ratios of 20I:10C, 15I:15C, and 10I:20C. Even with this limitation, all MOF/drug composites displayed rapid pharmacokinetic release rates signifying that dual-drug impregnation did not inhibit the release of the drugs from the carrier. In this regard, this work serves as an important proof-of-concept in that it demonstrates the possibility of rapid dual-drug release from a single MOF carrier, which has implications in addressing complex medicinal problems. As such, this study provides a simple and facile approach through which to administer multiple pharmaceutical compounds and demonstrates an important advancement for alternative drug delivery platforms. In future studies, it is necessary to modify the MOF textural properies for better control of the dual-drug loadings and to assess the in vitro performance of these materials in efforts of validating the biocompatibility of these materials. Altogether, such studies will help unlock the potential of our dual-delivery systems as alternative candidates for drug delivery tablets.

AUTHOR INFORMATION

Corresponding Author

Fateme Rezaei − *Department of Chemical & Biochemical Engineering, Missouri University of Science and Technology, Rolla, Missouri 65409-1230, United States;* orcid.org/0000-0002-4214-4235; Email: rezaeif@mst.edu

Authors

Shane Lawson − *Department of Chemical & Biochemical Engineering, Missouri University of Science and Technology, Rolla, Missouri 65409-1230, United States*

Ali A. Rownaghi − *Department of Chemical & Biochemical Engineering, Missouri University of Science and Technology, Rolla, Missouri 65409-1230, United States;* orcid.org/0000-0001-5228-5624

Complete contact information is available at: https://pubs.acs.org/10.1021/acsabm.1c01067

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors acknowledge Kyle Newport and Qasim Al-Naddaf for assisting with materials synthesis and characterization.

REFERENCES

(1) Huang, X.; Brazel, C. S. On the Importance and Mechanisms of Burst Release in Matrix-Controlled Drug Delivery Systems. *J. Controlled Release* **2001**, *73*, 121−136.

(2) Scarano, W.; de Souza, P.; Stenzel, M. H. Dual-Drug Delivery of Curcumin and Platinum Drugs in Polymeric Micelles Enhances the Synergistic Effects: A Double Act for the Treatment of Multidrug-Resistant Cancer. *Biomater. Sci.* **2015**, *3*, 163−174.

(3) Williams, I. M.; Wallom, K. L.; Smith, D. A.; Al Eisa, N.; Smith, C.; Platt, F. M. Improved Neuroprotection Using Miglustat, Curcumin and Ibuprofen as a Triple Combination Therapy in Niemann-Pick Disease Type C1Mice. *Neurobiol. Dis.* **2014**, *67*, 9−17.

(4) Popova, M.; Trendafilova, I.; Szegedi, A.; Momekova, D.; Mihaly, J.; Momekov, G.; Kiss, L. F.; Lazar, K.; Koseva, N. Novel SO_3H Functionalized Magnetic Nanoporous Silica/Polymer Nanocomposite as a Carrier in a Dual-Drug Delivery System for Anticancer Therapy. *Microporous Mesoporous Mater.* **2018**, *263*, 96−105.

(5) Wong, B. S.; Yoong, S. L.; Jagusiak, A.; Panczyk, T.; Ho, H. K.; Ang, W. H.; Pastorin, G. Carbon Nanotubes for Delivery of Small Molecule Drugs. *Adv. Drug Delivery Rev.* **2013**, *65* (15), 1964−2015.

(6) Amorim, R.; Vilaça, N.; Martinho, O.; Reis, R. M.; Sardo, M.; Rocha, J.; Fonseca, A. M.; Baltazar, F.; Neves, I. C. Zeolite Structures Loading with an Anticancer Compound as Drug Delivery Systems. *J. Phys. Chem. C* **2012**, *116* (48), 25642−25650.

(7) Wen, X.; Yang, F.; Ke, Q. F.; Xie, X. T.; Guo, Y. P. Hollow Mesoporous ZSM-5 Zeolite/Chitosan Ellipsoids Loaded with Doxorubicin as PH-Responsive Drug Delivery Systems against Osteosarcoma. *J. Mater. Chem. B* **2017**, *5* (38), 7866−7875.

(8) Lawson, S.; Newport, K.; Schueddig, K.; Rownaghi, A. A.; Rezaei, F. Optimizing Ibuprofen Concentration for Rapid Pharmacokinetics on Biocompatible Zinc-Based MOF-74 and UTSA-74. *Mater. Sci. Eng., C* **2020**, *117*, 111336.

(9) Singco, B.; Liu, L. H.; Chen, Y. T.; Shih, Y. H.; Huang, H. Y.; Lin, C. H. Approaches to Drug Delivery: Confinement of Aspirin in MIL-100(Fe) and Aspirin in the de Novo Synthesis of Metal-Organic Frameworks. *Microporous Mesoporous Mater.* **2016**, *223*, 254−260.

(10) Chen, Q.; Chen, Q. W.; Zhuang, C.; Tang, P. P.; Lin, N.; Wei, L. Q. Controlled Release of Drug Molecules in Metal−Organic

Framework Material HKUST-1. *Inorg. Chem. Commun.* **2017**, *79*, 78−81.
(11) Pei, P.; Tian, Z.; Zhu, Y. 3D Printed Mesoporous Bioactive Glass/Metal-Organic Framework Scaffolds with Antitubercular Drug Delivery. *Microporous Mesoporous Mater.* **2018**, *272*, 24−30.
(12) Lawson, S.; Newport, K.; Pederniera, N.; Rownaghi, A. A.; Rezaei, F. Curcumin Delivery on Metal−Organic Frameworks: The Effect of the Metal Center on Pharmacokinetics within the M-MOF-74 Family. *ACS Appl. Bio Mater.* **2021**, *4*, 3423−3432.
(13) Su, H.; Sun, F.; Jia, J.; He, H.; Wang, A.; Zhu, G. A Highly Porous Medical Metal−Organic Framework Constructed from Bioactive Curcumin. *Chem. Commun.* **2015**, *51*, 5774−5777.
(14) Glover, T.; Peterson, G. W.; Schindler, B. J.; Britt, D.; Yaghi, O. MOF-74 Building Unit Has a Direct Impact on Toxic Gas Adsorption. *Chem. Eng. Sci.* **2011**, *66* (2), 163−170.
(15) Wu, X.; Bao, Z.; Yuan, B.; Wang, J.; Sun, Y.; Luo, H.; Deng, S. Microwave Synthesis and Characterization of MOF-74 (M = Ni, Mg) for Gas Separation. *Microporous Mesoporous Mater.* **2013**, *180*, 114−122.
(16) Yang, D. A.; Cho, H. Y.; Kim, J.; Yang, S. T.; Ahn, W. S. CO_2 Capture and Conversion Using Mg-MOF-74 Prepared by a Sonochemical Method. *Energy Environ. Sci.* **2012**, *5* (4), 6465−6473.
(17) Rodrigues, N. M.; Martins, J. B. L. Theoretical Evaluation of the Performance of IRMOFs and M-MOF-74 in the Formation of 5-Fluorouracil@MOF. *RSC Adv.* **2021**, *11* (49), 31090−31097.
(18) Lawson, S.; Siemers, A.; Kostlenick, J.; Al-Naddaf, Q.; Newport, K.; Rownaghi, A. A.; Rezaei, F. Mixing Mg-MOF-74 with Zn-MOF-74: A Facile Pathway of Controlling the Pharmacokinetic Release Rate of Curcumin. *ACS Appl. Bio Mater.* **2021**, *4*, 6874.
(19) Han, Z.; Lu, L.; Wang, L.; Yan, Z.; Wang, X. Development and Validation of an HPLC Method for Simultaneous Determination of Ibuprofen and 17 Related Compounds. *Chromatographia* **2017**, *80* (9), 1353−1360.
(20) Doadrio, A. L.; Sousa, E. M. B.; Doadrio, J. C.; Pérez Pariente, J.; Izquierdo-Barba, I.; Vallet-Regí, M. Mesoporous SBA-15 HPLC Evaluation for Controlled Gentamicin Drug Delivery. *J. Controlled Release* **2004**, *97* (1), 125−132.
(21) Thommes, M.; Kaneko, K.; Neimark, A. V.; Olivier, J. P.; Rodriguez-Reinoso, F.; Rouquerol, J.; Sing, K. S. W. Physisorption of Gases, with Special Reference to the Evaluation of Surface Area and Pore Size Distribution (IUPAC Technical Report). *Pure Appl. Chem.* **2015**, *87*, 1051−1069.
(22) Sun, H.; Ren, D.; Kong, R.; Wang, D.; Jiang, H.; Tan, J.; Wu, D.; Chen, S.; Shen, B. Tuning 1-Hexene/n-Hexane Adsorption on MOF-74 via Constructing Co-Mg Bimetallic Frameworks. *Microporous Mesoporous Mater.* **2019**, *284*, 151−160.
(23) Mohan, P. R. K.; Sreelakshmi, G.; Muraleedharan, C. V.; Joseph, R. Water Soluble Complexes of Curcumin with Cyclodextrins: Characterization by FT-Raman Spectroscopy. *Vib. Spectrosc.* **2012**, *62*, 77−84.
(24) Gangwar, R. K.; Dhumale, V. A.; Kumari, D.; Nakate, U. T.; Gosavi, S. W.; Sharma, R. B.; Kale, S. N.; Datar, S. Conjugation of Curcumin with PVP Capped Gold Nanoparticles for Improving Bioavailability. *Mater. Sci. Eng., C* **2012**, *32* (8), 2659−2663.
(25) Mucha, M.; Mucha, M. Ibuprofen and Acetylsalicylic Acid Biosorption on the Leaves of the Knotweed: Fallopia x Bohemica. *New J. Chem.* **2017**, *41* (16), 7953−7959.
(26) Sogias, I. A.; Williams, A. C.; Khutoryanskiy, V. V. Chitosan-Based Mucoadhesive Tablets for Oral Delivery of Ibuprofen. *Int. J. Pharm.* **2012**, *436* (1−2), 602−610.
(27) Saravanan, M.; Bhaskar, K.; Srinivasa Rao, G.; Dhanaraju, M. D. Ibuprofen-Loaded Ethylcellulose/Polystyrene Microspheres: An Approach to Get Prolonged Drug Release with Reduced Burst Effect and Low Ethylcellulose Content. *J. Microencapsulation* **2003**, *20* (3), 289−302.
(28) Latifi, L.; Sohrabnezhad, S. Drug Delivery by Micro and Meso Metal-Organic Frameworks. *Polyhedron* **2020**, *180*, 114321.
(29) Rojas, S.; Colinet, I.; Cunha, D.; Hidalgo, T.; Salles, F.; Serre, C.; Guillou, N.; Horcajada, P. Toward Understanding Drug Incorporation and Delivery from Biocompatible Metal-Organic Frameworks in View of Cutaneous Administration. *ACS Omega* **2018**, *3* (3), 2994−3003.

https://doi.org/10.1021/acsabm.1c01067
ACS Appl. Bio Mater. 2022, 5, 265−271