

DESIGN OF METAL-ORGANIC FRAMEWORKS WITH BACKBONE-COORDINATED MEDICATIONS TOWARDS MULTIDRUG DELIVERY APPLICATIONS

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Abstract

The poor physiological solubilities and pharmacokinetics of small molecule active pharmaceutical ingredients (APIs) can be overcome using drug delivery systems (DDSs) with tunable properties. Metal-organic frameworks (MOFs) are porous, crystalline materials that are promising DDSs due to their periodic structure and customizable metrics. In this work, MOFs were synthesized with one API loaded into the pore environments while a second API was incorporated into the backbone of the MOF structure. Using two allopurinol (ALP) based MOFs, the loading and release profiles of two nonsteroidal-antiinflammatory drugs (NSAIDs) and ALP were studied using nuclear magnetic resonance spectroscopy and high-performance liquid chromatography. Of all tested formulations, a maximum encapsulation efficiency of approximately 10.7 % after 24 hours of loading was achieved using nabumetone, a prescription NSAID. The subsequent drug release showed complete NSAID release within the first 2 hours while ALP eluted over 24 hours.

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Keywords: Drug Delivery, Metal-Organic Frameworks, multidrug, allopurinol.

Received: August 24, 2026 Accepted: September 3, 2026 Revision Received: September 4, 2026 Published: September 16, 2026

Introduction

Advancements in drug delivery have been a focus of pharmaceutical research for the past 40 years. Design of specific delivery “vehicles” allows careful tuning of pharmacokinetic, pharmacodynamic, toxicity, and release patterns of active pharmaceutical ingredients (APIs).¹⁻³ Many APIs have poor bioavailability due to their hydrophobic, small molecular structures, thus delivery vehicles can increase efficacy of these drugs by increasing the clearance rate by balancing pharmacological effect and toxicity.^{4,5} Selective design of a drug delivery system (DDS) can also control the “burst release effect”, the phenomenon where a large majority of API is released rapidly upon administration.⁶ Co-crystallization of APIs with specific cofomers allows modification of pharmacochemical properties such as solubility, stability, and dissolution rate compared to pure API crystals.^{7,8} However, designing co-crystallization systems is still challenging as the specific intermolecular interactions between different compounds is difficult to predict.⁸ Furthermore, co-crystallization with multiple APIs for multidrug delivery are rare.⁹ For this reason, drug delivery vehicles that encapsulate APIs, such as lipid nanoparticles, liposomes, silica, and carbon nanotubes, are readily explored for multidrug delivery applications.¹⁰

Metal-organic frameworks (MOFs) are an emerging class of materials with particularly promising features for drug delivery applications. A MOF is a porous, crystalline material with a periodic structure composed of metal ions linked by organic molecules. The MOF structure and internal pore environments can be tuned in a predictable manner owing to reticular chemistry, where ligands with ancillary functional groups or variable lengths can be incorporated without disturbing the overall topology of the framework.¹¹ By adjusting the functionality or lengths of bridging linker molecules, the hydrophobicity, size, and acidity of the pores can be carefully controlled. Furthermore, several methods for controlling crystallite sizes down to nanoscale regime (<150 nm) have been developed to improve dispersability throughout biological systems.¹² The predictable and tunable natures of MOFs combined with the utilization of biocompatible metals such as Zn, Cu, Mg,

and Fe makes them prime candidates for drug delivery applications.¹²⁻¹⁶ MOFs also show promise in targeted delivery applications, delivering medication to specific tissues.^{17, 18}

The vast majority of DDSs reported in the literature focus on the loading and release of a single API. However, many ailments requiring medical intervention are treated with several medications simultaneously or cause secondary effects that need counteracting medications, including heart disease, obesity, hypertension, and osteoarthritis treatments.¹⁹ Another example is gout, a common inflammatory condition characterized by the deposition of monosodium urate in joint spaces.²⁰⁻²² The intense pain caused when these needle-like crystals localize in the knuckles of hands or feet result in debilitation from everyday motions, requiring prompt treatment.²¹ Common contemporary treatments use non-steroidal anti-inflammatories (NSAIDs), such as ibuprofen and naproxen, for pain and inflammation alleviation and etiological treatment with urate lowering therapy (URT), such as allopurinol (ALP), colchicine medications or corticosteroid injections into the joint space.²⁰ Generally, NSAIDs are small, hydrophobic molecules that can cause significant negative side effects when taken orally, namely ulceration and bleeding in the gastrointestinal system.⁹ Thus, gout treatment serves as an ideal model for investigating a DDS for multidrug delivery from a single formulation as a novel treatment method to improve patient outcomes and decrease side effects.

When developing a therapy using multidrug delivery from a single DDS, it is crucial to consider the release kinetics of the respective drugs for the specific medical condition. For example, there may be cases when rapid release rates for both APIs are preferred to slower or differentiable rates. In gout treatment, we envision a burst release of NSAID to provide quick symptomatic relief with a simultaneous but gradual release of ALP to control flareups over time. We hypothesized that pore-loaded MOF strategies combined with co-crystallization techniques would allow increased control of pharmacochemical properties of the APIs in a DDS. Incorporating ALP into the backbone of the MOF would

constrain its release to the MOF degradation while an NSAID localized within the pores would readily diffuse out of the structure due to comparatively weaker interactions (**Scheme 1**). MOFs with APIs as bridging ligands are rare²³⁻²⁶, and in those selective cases the simultaneous release of additional pore-bound APIs were not investigated, providing an opportunity to investigate the efficacy of the proposed design.²⁷

Two metal-organic frameworks with ALP substituted backbones have been reported to date, both of which include a secondary dicarboxylate linker to increase the dimensionality of the resultant structure.^{28,29} An over-the-counter and prescription NSAID were selected and their uptakes into the MOF pores were studied. Drug-elution differences between the pore-abiding NSAID and covalently bound ALP were compared using liquid chromatography. The weaker, non-covalent interactions within the pores resulted in a faster elution time for one of the NSAIDs compared to the Zn-coordinated ALP within the framework. Since the ALP is coordinated to the metals within the MOF, the effective ALP concentration can be tuned by changing the mass of MOF administered. Contrastingly, the NSAID could be varied by altering the conditions of the drug-loading step, thus enabling tailored treatments for specific patients based on severity of the condition.

Experimental Methods

ALP-MOF-1 ($[Me_2NH_2][Zn_3(AlP)(TDC)_{2.5}]$) Synthesis

A modified version of the literature procedure was used to synthesize this material.²⁸ Stock solutions (20 mL) of the following compounds were prepared in N,N-dimethylformamide (DMF, 99.8+%, Thermo Scientific): 0.05 M zinc acetate dihydrate (1.00 mmol, 0.219 g, 98%, extra pure, Thermo Scientific), 0.05 M allopurinol (1.00 mmol, 0.136 g, “ALP”, $C_5H_4N_4O$, >98.0%, TCI), and 0.05 M 2,5-thiophenedicarboxylic acid (1.00 mmol, 0.172 g, “TDC”, $C_6H_4O_4S$, >98%, TCI). In a 20 mL glass vial, 2 mL of the $Zn(CH_3COO)_2 \cdot 2H_2O$ solution, 1 mL of the ALP solution, and 4 mL of the TDC solution were added, followed by 3.7 mL of additional DMF. The cloudy solution was capped and kept in a 95°C oven for 16 hours. Once removed, the solution was decanted and the remaining crystals were washed several times with 10 mL of fresh DMF. Solvent washing was repeated three times per day for three days, then stored in DMF for later use.

ALP-MOF-2 ($Zn_2(\mu_2-H_2O)(AlP)(BDC)$) Synthesis

A modified version of the literature procedure was used to synthesize this material.²⁹ Dry DMF used in this synthesis was prepared by drying over molecular sieves overnight (Dry DMF, Sigma Aldrich). Zinc nitrate hexahydrate (3.00 mmol, 0.892 mg, 98%, extra pure, Thermo Scientific) and sodium acetate trihydrate

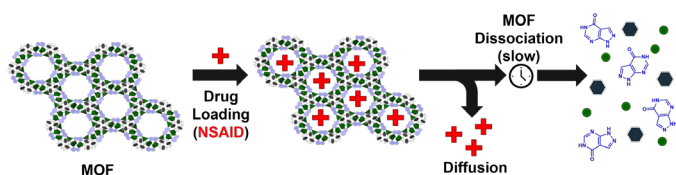
(3.00 mmol, 0.408 g, Fisher Chemical), were dissolved in dry DMF and nanopure water (NP, Thermo Scientific Barnstead Gen-Pure, 18.2 M Ω ·cm), respectively, to make a 0.15 M stock solutions (20 mL). Additionally, ALP (1.00 mmol, 0.136 g) and terephthalic acid (1.00 mmol, 0.166 g, “BDC”, $C_8H_6O_4$, >99.0%, TCI) were each dissolved in dry DMF to make 0.05 M stock solutions (20 mL). To a 100 mL Schott bottle, 3 mL of $Zn(NO_3)_2$ solution, 6 mL of ALP solution, 6 mL of ALP solution, 6 mL of BDC solution, and 3 mL of $NaCH_3COO$ solution were added followed by 3 mL of dry DMF, 18 mL of N,N-dimethylacetamide (DMA, C_4H_9NO , 99+%, Thermo Scientific), and 3 mL of NP water were added to the bottle. The reaction mixture turned cloudy upon addition of $NaCH_3COO$. The bottle was kept in a 100 °C oven for 18 hours. The washing procedure was the same as the ALP-MOF-1 procedure.

MOF Characterization

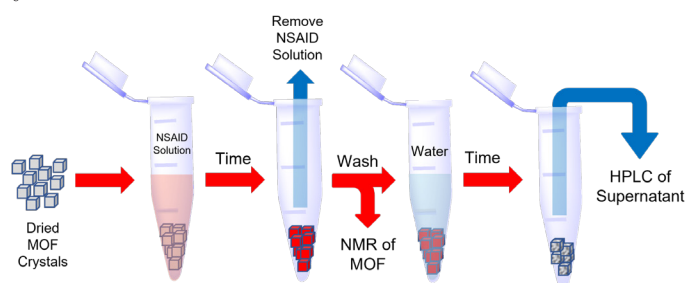
After washing crystals thoroughly with DMF, morphology of the ALP-MOFs were examined using optical microscopy (Laxco LMI 3000). Crystalline phase of the products was characterized by powder X-ray diffraction (PXRD, Bruker D2 Phaser) using a $Cu\ K\alpha_1$ line (1.540598 Å) at 30 kV and 10 mA. Ligand ratios and drug content were confirmed using ^1H NMR (JEOL 400 MHz) using mesitylene in d_6 -DMSO (Cambridge Isotope) as an internal standard. Attenuated total reflectance-Fourier transform infrared spectroscopy (ATR-FTIR, Thermo Fisher iS50) was collected on crystals after washing and drying. Drug elution studies were completed using high-performance liquid chromatography (HPLC, Agilent Technologies 1200 Series) equipped with a DAD detector and a C18 column (3 μm , 4.6 mm x 100 mm). The detection wavelength was set to 222 nm and the mobile phase was a gradient elution of water and acetonitrile with a flow rate of 1 mL/min at room temperature.

Drug loading

Drug loading and release procedures are summarized in **Scheme 2**. Wet DMF was used to prepare 0.1 M solutions of both NSAIDs at 37 °C. In a 1.5 mL Eppendorf tube, 10 mg of dried MOF crystals and 1 mL of either a saturated nabumetone (NAB) or ibuprofen (IBU) solution was added. The tubes were mixed at 37 °C at 500 rpm using a thermomixer. Tubes were taken off the thermomixer at 24, 48, and 72 hour time points. NSAID solutions were refreshed every 24 hours. Once taken off the thermomixer, NSAID solutions were removed and the crystals were quickly washed twice with fresh DMF. The samples were then dried under vacuum on a Schlenk line. Once dry, NMR samples were made using at least 3.0 mg of MOF, 0.6 mL of d_6 -DMSO, and 10 μL of DCl to dissolve the MOF. A 0.240 M solution of mesitylene in d_6 -DMSO was used as an internal standard. A mass ratio of 1:2 of



Scheme 1. Design of multidrug delivery in ALP-MOFs with NSAIDs loaded into the pores. NSAIDs quickly diffuse out of the pores while ALP is delivered over time as the MOF degrades in solution. NSAIDs, ALP, Zn, and dicarboxylate linkers are represented by red pluses, blue molecules, green circles, and black hexagons, respectively.



Scheme 2. Simplified procedure for preparing NSAID-loaded ALP-MOFs and subsequent characterization of the drug release properties.

MOF to internal standard was used to determine the moles of ALP in each sample.

Drug Release

Following drug loading, ALP-MOF crystals were washed and dried. Then 1 mL of NP water was added to each Eppendorf tube. The tubes were set on the thermomixer at 37 °C and mixed at 500 rpm. The tubes were taken off the thermomixer after 2, 4, 8, 16, and 24 hour time intervals. The supernatant was then collected and stored in screw thread vials for HPLC analysis. The samples were placed on the autosampler and a needle washing procedure using 100% acetonitrile was used between each sample injection. Quantifiable results including retention time, peak intensity, peak height, and peak area were generated and used for further analysis.

Results and Discussion

An initial literature search revealed only two MOF structures containing ALP as a coordinating ligand, hereby referenced as ALP-MOF-1 and ALP-MOF-2.^{28,29} The asymmetric unit of ALP-MOF-1 contains five molecules of TDC and two ALP ligands coordinated to three unique Zn²⁺ sites (**Fig. 1a**). The resultant framework is anionic and the charge is balanced by dimethyl ammonium ions within the pores (**Fig. 1b**). When extended in three dimensions, three distinct pore environments are formed (**Fig. 1c**). ALP-MOF-2 contains repeating clusters of four Zn²⁺ bridged by both ALP and BDC linkers (**Fig. 1d**), resulting in large channel-like pores along the c-direction (**Figs. 1e,f**). Only compounds smaller than the pore apertures of the MOFs can be drawn into the material, so the pore volumes and respective apertures were carefully studied to screen potential NSAIDs for drug loading. Based on the reported crystal structures, ALP-MOF-1 and ALP-MOF-2 contain a total porosity of 0.188 and 0.201 cm³/g, respectively. The apertures separating the pores of ALP-MOF-1 were measured as 9.382 Å x 8.884 Å, 4.447 Å x 4.952 Å, and 8.525 Å x 5.334 Å. The large channels of ALP-MOF-2 have a diameter of 9.819 Å with additional apertures of 6.373 Å running perpendicular to the

channels. Therefore, we selected ibuprofen (IBU) and nabumetone (NAB) (**Figs. 1g,h**) as our model NSAIDs due to their compatible dimensions.

Rigorous characterization was employed to confirm the composition and crystalline phase of the desired ALP-MOFs. Optical images of the colorless crystals showed unique habits, where the ALP-MOF-1 formed elongated dodecahedron (**Fig. 2a**) crystals and ALP-MOF-2 appeared as twisted blocks (**Fig. 2b**). Incorporation of all reagents into the MOFs were verified using ATR-FTIR spectroscopy. Carbonyl stretches at approximately 1697 cm⁻¹ and aromatic C-H stretches around 3073 cm⁻¹ of ALP were maintained in the spectra of both ALP-MOFs (**Fig. 2c, 2d**). The predominant carbonyl stretch of TDC at 1651 cm⁻¹ was observed in ALP-MOF-1 while those of BDC were shifted from 1670 cm⁻¹ to 1607 cm⁻¹, indicating pi-backbonding between the ligands and the metals and thus successful coordination. For additional compositional analysis, ¹H NMR was used to verify the ligand ratios matched the reported crystal structure. Both MOFs showed lower quantities of ALP compared to the expected ratios of ALP:TDC (1:2.5) and ALP:BDC (1:1) for ALP-MOF-1 and ALP-MOF-2, respectively. This excess of dicarboxylate ligands is likely due to crystalline faces preferentially terminating with chelating dicarboxylate ligands as opposed to ALP to more effectively reduce the surface energy of the unsaturated metal sites. Charge-balancing dimethyl ammonium ions were also observed in ALP-MOF-1 in the expected stoichiometric amount. In both ALP-MOFs, residual solvent and acetate were apparent. Dried crystals were also subjected to PXRD analysis and compared to diffraction patterns of the reported structures from the literature. The respective patterns showed almost complete matches, implying successful synthesis of the desired products even with modified syntheses. In totality, these results indicate the successful synthesis of both ALP-MOFs (**Fig 3a, 3b**).

Because the release of ALP accompanies the dissociation of the ALP-MOF crystals, elucidating the solvothermal stability of the MOFs is essential. Solutions with varying polarity, pH, and temperature were used to assess the stability of the ALP-MOFs with the ultimate goal of mimicking physiological conditions.

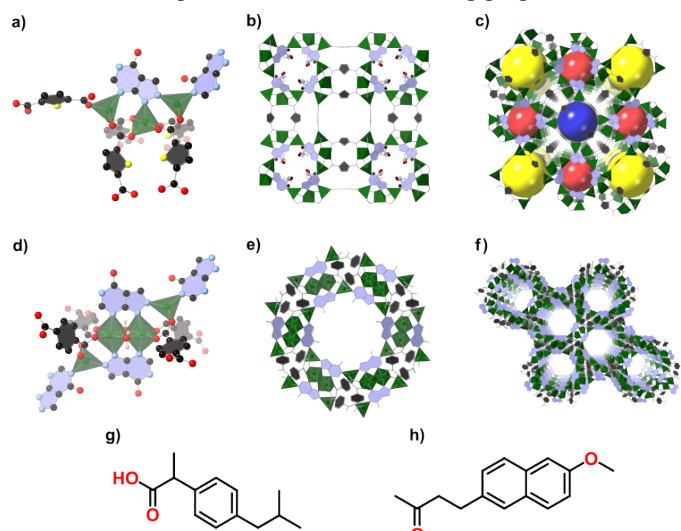


Figure 1. Connectivity and porosity of ALP-MOF-1 and ALP-MOF-2 (a-f). Charge-balancing dimethyl ammonium ions are located near the ALP-lined pores of ALP-MOF-1 in b). Red, green, light blue, yellow, pink, and dark gray spheres represent oxygen, zinc, nitrogen, sulfur, hydrogen, and carbon atoms, respectively. The large colored spheres in c) illustrate the three unique pores of ALP-MOF-1. Molecular structures of g) IBU and h) NAB.

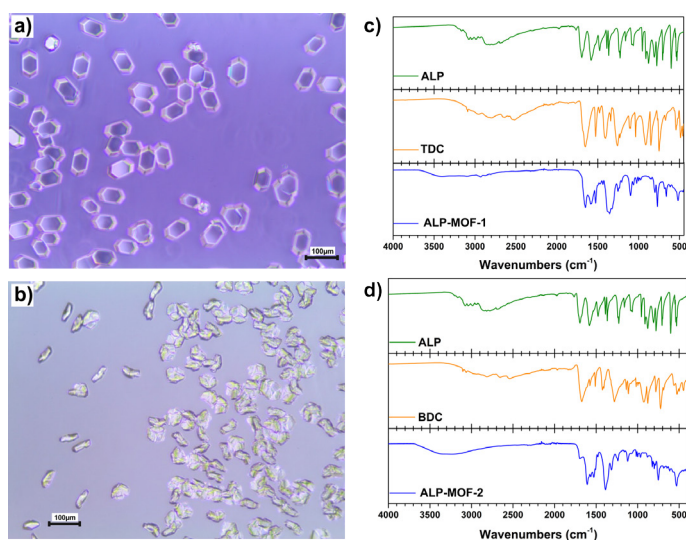


Figure 2. Microscope images of a) ALP-MOF-1 and b) ALP-MOF-2. FTIR characterization of organic ligands and the resulting crystalline products of c) ALP-MOF-1 and d) ALP-MOF-2.

ALP-MOF crystals were soaked in either DMF, NP water, or phosphate-buffered saline (PBS) while incubating at 25 °C or 37 °C for various time intervals. The crystals were removed and washed several times with fresh DMF before collecting PXRD scans. Both ALP-MOFs showed no signs of degradation after soaking in DMF at 25 °C and 37 °C for up to 72 hours. However, a change in the XRD patterns of all ALP-MOFs was observed after soaking in water and PBS for 72 hours. This result likely signifies the transition to new, unknown, crystalline phases likely containing exclusively Zn and ALP. Regardless of the final structure, it is clear that the ALP-MOFs decompose within 24 hours of soaking in both water and PBS at 37 °C.

Informed by the stability studies, NSAIDs were loaded into the pores of the ALP-MOFs under a series of conditions to ascertain the maximum loading capacity. It is important to state that since the ALP is incorporated into the framework of the MOFs, the quantity of ALP is directly proportional to the mass of MOF used. Based on the stoichiometry of ALP in both MOFs, the ALP content is 0.181 and 0.300 g/g for ALP-MOF-1 and ALP-MOF-2, respectively. To promote diffusion into the ALP-MOFs, the crystals were mixed at 37 °C in saturated solutions of IBU and NAB in DMF and were replaced every 24 hours. Once removed from temperature and stirring, the samples were washed quickly with DMF twice to remove free or surface-adsorbed NSAIDs. After washing, the loaded MOF crystals were dried and prepared for NMR analysis. Mesi-

tylene was added as an internal standard as it has easily observable and quantifiable peaks in both the aromatic and aliphatic chemical shift regions. Since the exact concentration of the mesitylene added to the NMR sample was known, the exact amount of NSAID can be determined by comparing peak integrations and converting to grams to determine the encapsulation efficiency (Equation 1).

$$\text{Encapsulation Efficiency} = \frac{\text{Mass of NSAID}}{\text{Mass of NSAID} + \text{Mass of MOF}} \quad (1)$$

Results from the NMR analysis of drug loading in both ALP-MOFs revealed no significant variation by time, indicating a maximum drug adsorption into the pores was achieved within the first 24 hours. The maximum encapsulation efficiency of IBU and NAB in ALP-MOF-1 was determined to be 7.88% and 10.07% after 24 hours, respectively (**Table 1**). Although the NAB molecules are larger and more rigid than IBU, they likely form stacks within the pores of the MOF better than IBU, leading to higher adsorption. ALP-MOF-2 resulted in comparatively lower encapsulation efficiencies of IBU and NAB at 2.72% and 1.60%, respectively (**Table 1**). The overall lower uptake in ALP-MOF-2 was surprising considering the greater porosity and larger, more regular channel-like pores. It is hypothesized that the NSAID molecules are flowing through the pores and interacting with each other rather than spreading out across internal surface areas of the pores, thus blocking additional NSAIDs from entering the pores. Because ALP-MOF-1 has distinct pore sizes that can better entrap single NSAID molecules without blocking diffusive pathways, the overall loading capacity is higher.

Drug-loaded ALP-MOFs were then subjected to aqueous environments to characterize the release of ALP and NSAIDs using HPLC. Although PBS is a better mimic of bodily fluids for the desired application, water was selected as the drug release solvent based on compatibility with the HPLC column and the known instability of the MOFs over time. A gradient method for the HPLC was established by altering the percentages of water and acetonitrile over a period of 45 minutes to effectively separate the desired compounds. All samples were prepared in triplicate for each time point, NSAID drug, and ALP-MOF, resulting in a total of 60 samples. Using the established HPLC method, the expected retention times for dicarboxylate ligands, ALP, and the NSAID drugs were approximately 0.5, 3, and 20 minutes, respectively. Peak intensities at those times were used with internal calibration curves for all compounds to determine the concentrations of the eluted APIs.

The drug release profile of IBU in ALP-MOF-1 tracked almost identically with that of ALP (**Fig. 4a**). A steady increase in the concentration of eluted drugs was apparent within the first 8 hours of soaking in water at 37 °C. After this time point, a plateau was reached for both drugs at an average concentration of approximately 0.50 mM for ALP and 0.45 mM for IBU. The lack of distinct drug release profiles suggests the MOF was simply de-

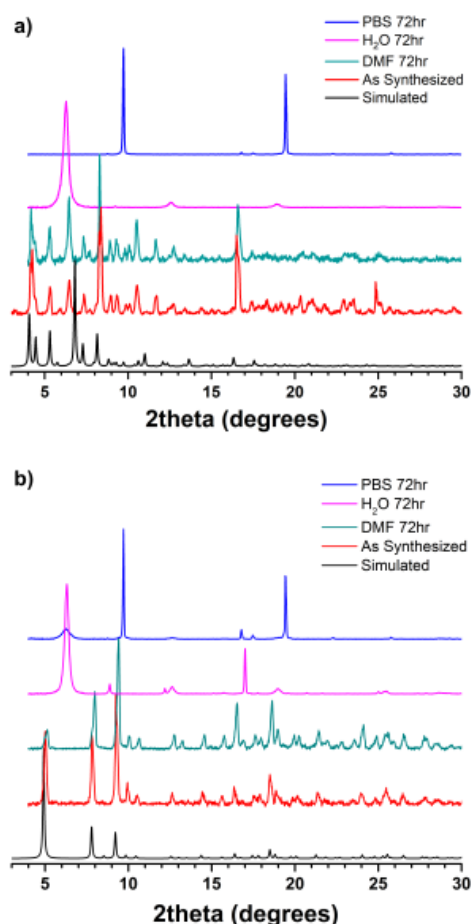


Figure 3. PXRD of synthesized a) ALP-MOF-1 and b) ALP-MOF-2 compared to the simulated pattern. Significant changes to the powder patterns were observed after soaking in PBS and NP water for 72 hours, likely indicating a transition to a different crystal structure.

Table 1. Average encapsulation efficiency of ALP-MOFs using IBU and nabmentone. ALP content is based on stoichiometry of each MOF.

	Average NAB Uptake (g/g)	Loading capacity, NAB (Std. Dev)	Average IBU uptake (g/g)	Loading capacity, IBU (Std. Dev)	ALP Content (g/g)
ALP MOF-1	0.112	10.7% (± 0.76)	0.0858	7.88% (± 1.41)	0.170
ALP MOF-2	0.0163	1.60% (± 0.16)	0.0280	2.72% (± 0.24)	0.304

grading in solution, thus releasing the coordinated ALP and IBU simultaneously. The authors hypothesize that this relatively quick decomposition may be due to the diffusion of charge-balancing dimethylammonium ions out of the MOF, destabilizing the entire framework and promoting a change to a neutral compound. Comparatively, NAB-loaded ALP-MOF-1 demonstrated an immediate and complete release of NAB (Fig. 4b). After two hours in water at physiological temperature, the NAB concentration of the supernatant was approximately 0.05 mM and this concentration was maintained for every additional time point over the 24 hour testing period. While the ALP concentration over time follows a similar pattern to that observed with the IBU-loaded MOF, several discrepancies were observed. The concentration at the 4 hour time point was approximately half of that observed at 2 hours. Furthermore, a more gradual release of ALP was observed as the concentrations at 8 and 16 hours averaged near 0.25 mM. This could potentially be explained by the presumably weaker interactions between NAB and the ALP-MOF, where the diffusion out of the pores does not destabilize the MOF as much as the removal of IBU from the pores.

The drug release profiles of ALP-MOF-2 were similar to those results found in ALP-MOF-1. For the IBU-loaded MOF, the release profiles of both APIs show almost identical behaviors over a 24 hour period (Fig. 5a). A key difference is a small, initial plateau at 0.14 and 0.084 mM for IBU and ALP, respectively, within the first four hours. A subsequent increase in concentration follows at longer time points until a second and final plateau is observed at 0.45 and 0.31 mM. The observed profiles may suggest that the MOF may be initially stabilized by the replacement of IBU with water molecules within the pores, which is supported by the hydrophilic nature of the MOF.²⁹ The release of NAB from ALP-MOF-2

was initially fast and consistent with the release profile observed in ALP-MOF-1 (Fig. 5b). However, large standard deviation at early time points indicates the total amount of NAB released is variable, likely depending on the extent of interactions between NAB within the pores. Significant pi-pi stacking interactions between adjacent NAB in the pores could inhibit the diffusion of water molecules, resulting in a decreased elution of the NSAID. The concentration of ALP in the supernatant was considerably reduced compared to the IBU-loaded ALP-MOF-2 samples. Moreover, the ALP concentration did not significantly change over the 24 hour period, suggesting that the MOF did not decompose appreciably. This result supports the hypothesis that the stronger interactions between the MOFs and IBU lead to destabilizing effects within the MOF once the IBU diffuses out of the pores.

These findings support the proposed design for multidrug delivery using API-coordinated MOFs. ALP-MOF-1 loaded with NAB best demonstrates the intended purpose of this DDS where two clear drug release profiles are observed for ALP and the NSAID. Although both NAB-loaded MOFs show a quick and complete release of the NSAID, ALP-MOF-2 does not show considerable release of the ALP over time, thus limiting its ability to deliver etiological relief in the desired application. Furthermore, the relatively low encapsulation efficiencies of ALP-MOF-2 reduce its efficacy for drug delivery applications. It is clear that when applying this strategy the strength of interactions between the MOF pores and the loaded NSAID should be carefully considered, as strongly interacting drugs can lead to accelerated decomposition of the MOF upon removal from the pores leading to immediate release of both compounds.

Conclusions

This study focused on the drug-elution differences between multiple APIs from within the pores and backbone of two different ALP-MOFs. The stability of the ALP-MOFs under various conditions were tested to determine the optimal conditions for drug loading and release. The maximum encapsulation efficiencies of two NSAIDs in two unique ALP-MOFs were determined and subsequent release of drugs in the presence of water were analyzed. Notably, only the NAB-loaded ALP-MOF-1 system resulted in the distinct drug release profiles between the coordinated and pore-abiding APIs. In this specific case, the API located within the pores were found to elute at a faster rate than the API incorporated into the backbone of the MOF, offering differentiable release profiles for the drugs within the same DDS. In the context of gout treatment, this material could provide a quick release of the NSAID within the first two hours of administration while ALP is released over the course of 24 hours for sustained inhibition of urate formation. These preliminary results show promise towards the ultimate application of multidrug delivery with tunable concentrations and differential drug release kinetics and could be adapted to any multidrug system with at least one API with structural characteristics amenable to bridging adjacent metal ions. Further studies to elucidate the crystal structures of the ALP-MOFs after soaking in water and PBS are planned. Additionally, investigation of the drug release kinetics in PBS are ongoing to determine the effect of more physiologically relevant media.

Acknowledgements

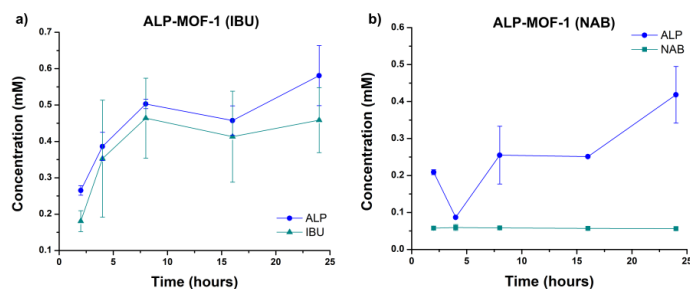


Figure 4. Drug elution profiles of a) IBU- and b) NAB-loaded ALP-MOF-1. ALP, IBU, and NAB concentrations are denoted by circular, square, and triangular data points, respectively. Error bars represent one standard deviation of the triplicate measurements for each time point.

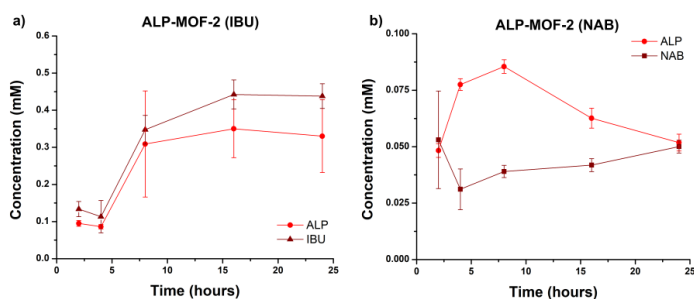


Figure 5. Drug elution profiles of a) IBU- and b) NAB-loaded ALP-MOF-2. ALP, IBU, and NAB concentrations are denoted by circular, square, and triangular data points, respectively. Error bars represent one standard deviation of the triplicate measurements for each time point.

The authors would like to thank Dr. Duane Weisshaar for helpful discussions and instrumentation guidance. This work was supported in part by the Augustana Department of Chemistry and Biochemistry and an Institutional Development Award (IDeA) from the National Institute of General Medical Sciences of the National Institutes of Health [P20GM103443]. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Health.

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