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Ti-Based nanoMOF as an Efficient Oral Therapeutic Agent

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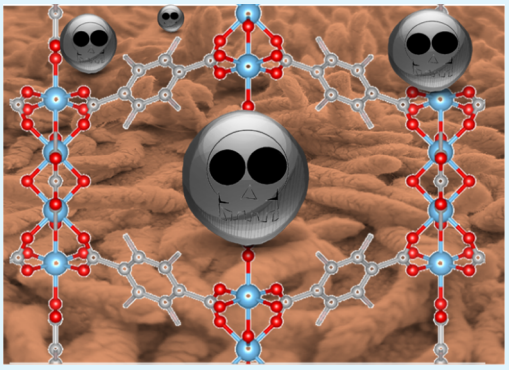
Supporting Information

ABSTRACT: Despite the interest in (Zn, Fe, and Zr)-nanoscaled metal−organic frameworks (nanoMOFs) as intravenous drug nanocarriers, their most convenient oral administration has been almost unexplored. In this scenario, an uncharted Ti-nanoMOF is originally proposed here as an oral therapeutic agent, not as a drug delivery system but as an innovative and efficient oral detoxifying agent of the challenge and timeliness salicylate intoxication (e.g., aspirin). Thus, this orally robust and biosafe Ti-nanoMOF is the only porous nanomaterial, among the six tested MOFs, able to adsorb and retain aspirin under the whole gastrointestinal tract, overpassing the capabilities of the current treatment (i.e., activated charcoal). Further, the biodistribution and bioremoval of Ti-nanoMOF have been assessed, proving a bioprotective character with an intact and almost complete removal by feces.



KEYWORDS: *metal−organic frameworks, drug overdose, nanoparticles, detoxification, salicylates, biosafety*

INTRODUCTION

Among the different nanomaterials proposed so far as therapeutic agents, nanoscaled metal−organic frameworks (nanoMOFs) have emerged as integrating platforms with promising capabilities. These porous coordination polymers, comprising inorganic nodes and organic linkers that assemble into multidimensional periodic lattices,[1] have been traditionally proposed in other fields (catalysis,[2] separation,[3] or drug delivery).[4,5] In the biomedical field, metal−organic frameworks (MOFs) have been mainly proposed for the controlled delivery of active ingredients (i.e., drugs, cosmetics, gases, etc.) or for the encapsulation of biomacromolecules.[6] Their outperforming properties (exceptional porosity, selective adsorption, tunable particle size and stability, biocompatibility, potential biodegradation and/or elimination avoiding accumulation, functionalization of their structure, etc.) made them suitable candidates as carriers of drug.

The vast majority of the investigations reported so far deal with the intravenous administration of (Zn, Fe, and Zr)-nanoMOFs. However, the most commonly used oral route is preferable as it provides the best comfort for patients, improving their compliance and treatment efficacy. To date, only two works have evaluated the use of *in vivo* orally administered MOFs (Cu-BTC and CD-MOF)[7,8] as drug delivery systems. Nevertheless, their unknown biodistribution and aqueous instability might limit their practical use.[9,10] In this scenario, we proposed here an original oral carrier based on a chemically robust Ti-based MOF that, to the best of our knowledge, has never been explored.

To further advance in the novel oral administration of a Ti-MOF while proving its potential in a highly innovative and challenging area, this work proposes a new tool for the treatment of oral intoxications. In this sense, accidental or intentional drug overdoses are considered as a major public health problem.[11] Drug overdoses are the leading cause of injury deaths, especially among young people (e.g., 72 000 and 7600 people died in the USA and EU in 2017, respectively).[12,13] Current detoxification therapies (i.e., activated charcoal (AC), antidotes, cathartics) are inefficient as many patients continue suffering and/or dying from intoxication. They exhibit important drawbacks such as lack of selectivity, poor affinity for some toxins, and associated severe adverse effects.[14−18] As a promising alternative, the proof of concept of a new oral detoxifying tool has been very recently provided using a micrometric Fe-based MOF (or MIL-127) with promising performances.[19] However, the biodistribution of the toxic molecule and the MOF was not addressed. Further, to go a step forward and demonstrate the real potential of MOFs for both oral detoxification and drug delivery, we need to determine the main parameters (e.g., MOFs' particle size and composition, gastrointestinal (GI) stability and absorption kinetics, dose) governing the oral detoxification process by MOF.

Herein, a pioneer complete kinetic study on the efficiency of a Ti-nanoMOF as a drug overload detoxifying agent was performed using two different MOF doses, comparing our results with the currently applied treatment. Also, the biodistribution of the drug and the nanoMOF (and its

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constituents) was exhaustively analyzed over time, evaluating also the GI protective effect and safety of the Ti-nanoMOF. It should be noted here that, to the best of our knowledge, there is no *in vivo* oral evaluation (biocompatibility, efficiency, etc.) of a Ti-based MOF, although this route is very convenient for detoxification but also therapy.[19]

Thus, we chose the tetragonal titanium(IV) aminotereph-thalate MIL-125-NH_2 or $Ti_8O_8(OH)_4(O_2C-C_6H_3NH_2-CO_2)_6$ as the nanoMOF, exhibiting several features that make it an excellent oral detoxifying candidate: (i) it is based on Ti (oral lethal dose LD_{50} = 25 g·kg^{-1}), which is considered the most biocompatible metal surpassed only by Fe (30 g·kg^{-1}), (ii) when orally administered, it has extremely low absorption;[20,21] (iii) it exhibits a large porosity (S_{BET} ≈ 1400 $m^2·g^{-1}$, V_p ≈ 0.6 $cm^3·g^{-1}$ with octahedral ∼12.5 Å and tetrahedral cavities ∼6 Å, accessible via windows ∼5−7 Å), which provides structural superiority for the encapsulation of drugs;[22] and (iv) it can be synthetized at the nanoscale (discs of 390 ± 94 × 241 ± 65 nm, n = 150), which make it interesting not only as an adsorbent of toxins but also as a drug delivery agent (complete characterization in Supporting Information, Section S3).[23]

On the other hand, as a toxic molecule, we selected the widely used anti-inflammatory and analgesic salicylate, aspirin (acetylsalicylic acid or ASA, molecular dimensions 7.8 × 5.8 × 2.3 Å calculated by density functional theory).[24] Although used as a model in this study, allowing an easy comparison with previously reported adsorbents[25] (including the novel MOF absorbent),[19] the challenge of ASA oral detoxification should be highlighted: >40 400 cases of human exposure were reported in the USA in 2004, of which 63% were unintentional exposures and 44% involved children younger than 6.[26] Moreover, the acetylsalicylic acid metabolite (i.e., salicylic acid) has been listed amongst the nine pediatric poisons which lead to death in children at low doses (150 mg·kg^{-1}; placed in perspective, one teaspoon contains 7000 mg of salicylate).[27] Apart from the high incidence and severe consequences of ASA overdose, no specific antidote is available. Although AC effectively avoids gastric absorption of the salicylate, its lack of retention under intestinal conditions makes necessary the administration of repeated doses (Multiple Dose AC) to avoid ASA GI absorption.[17] Gastric lavage may be used to evacuate the stomach in patients. Although it presents the same ASA elimination success as AC, it should not be performed routinely in all poisoned patients, taking a longer time to prepare than AC and producing patient discomfort.[28,29]

RESULTS AND DISCUSSION

GI Stability and Adsorption Capacity. Initially, the structural integrity of MIL-125-NH_2 was screened under mimicked GI conditions found in healthy vertebrates: first, suspending the solid in gastric media (HCl, pH = 1.2 at 37 °C for 2 h), followed by intestinal conditions (simulated intestinal media, SIF; pH = 6.8 at 37 °C for 24 h).[30] The results confirm that MIL-125-NH_2 keeps its crystalline structure and micro-porosity upon simulated GI conditions (Supporting Information Figure S4). These results prompt us to further evaluate the matrix chemical stability and the ASA adsorption capacity for oral administration, particularly for toxin removal. The release of the constitutive organic linkers and the remaining ASA was quantified by high-performance liquid chromatography (HPLC) in simulated overdose conditions by using two different amounts of MOF (ASA/MOF ratio = 1:0.5 in excess of the drug; and 1:2 in excess of the MOF; Figure 1 Supporting Information, Sections S2 and S4). It should be noted that

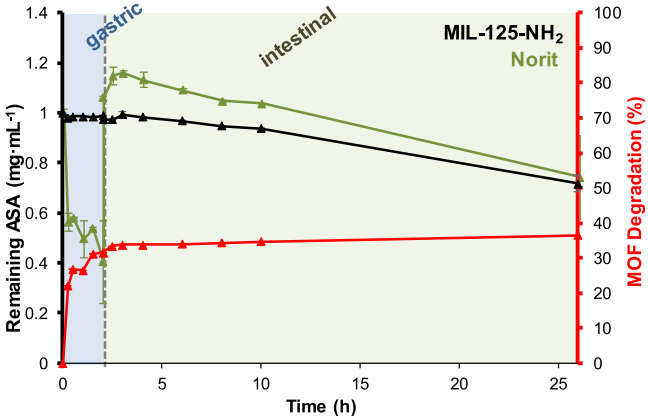

Figure 1. Comparative evolution of salicylate removal using MIL-125-NH_2 (left, black) and Norit@AC (left, green) using the same amount (mass) of adsorbent and the same ASA initial concentration under simulated GI conditions (the blue and green backgrounds represent gastric and intestinal media, respectively). The concentrations of salicylates have been normalized for an easier comparison. The MIL-125-NH_2 matrix degradation (right, red) was also represented.

because of the important GI hydrolysis of ASA to salicylic acid (SA),[19] both active (and toxic) salicylate derivatives were considered for the quantification (and denoted as ASA). To better assess the significance of our results, the same procedure was performed using other MOFs, widely studied as drug carriers (MIL-53(Fe),[31] MIL-53(Fe)-$(OH)_2$,[32] MIL-100-(Fe),[33] UiO-66(Zr),[34] UiO-66(Zr)−NH_2,[35] and ZIF-8(Zn))[36] and the current ASA detoxification method (Norit@activated carbon, see Supporting Information Section S2). Without exception, commercial Norit@activated carbon exhibits a higher efficiency of ASA removal under stomach conditions (2−13% using stable MOFs vs 97% using Norit@activated carbon, Figure 1, Table S2). However, as already known in clinics (also evidenced in our experiments; Figure 1), one of the main limitations in the current ASA detoxification treatments is the release of the adsorbed drug when it passes to the intestine,[37] decreasing its efficiency and requiring the administration of multiple consecutive doses.[17,38,39] This effect is observed in AC, resulting in a higher amount of toxin in the intestine maintained over 24 h (Figure 1). The release of the toxin, once in the intestine, is also observed in some tested MOFs (MIL-100, UiO-66, and UiO-66-NH_2), probably associated with an important matrix disintegration (% of leached ligand ∼90, 22 and 40%, respectively; Table S2, Figure S7). In this sense, although a partial degradation of MIL-125-NH_2 occurs under gastric conditions (∼30%, Figure 1), this solid is able to resist the GI harsh environment (total degradation ∼35%), supporting its interest for diverse oral treatments. It is also interesting to mention that the bypass from gastric to intestinal conditions is not associated with ASA. Therefore, MIL-125-NH_2 is the only MOF able to retain and adsorb ASA under intestinal conditions.

After 24 h, MIL-125-NH_2 eliminates up to 28 and 20% of the total ASA (ASA/MOF ratio = 1:0.5 and 1:2, respectively, Table S2). These values are comparable to the Norit@ activated carbon (26 and 34%, respectively)[19] and to those previously reached by MIL-127 (25 and 39%, ASA/MOF ratio

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1:0.33 and 1:0.66, respectively). However, if we consider the treatment of ASA overdose, of particular interest is the fact that the most efficient detoxifying dose of MIL-125-NH_2 corresponds to the highest amount of ASA, which is typically the case in fatal overdoses (>500 mg·kg^{-1}).[40] Taking all these results into account, the MIL-125-NH_2 material is the best performing ASA detoxifying agent. In terms of drug loading capacity, MIL-125-NH_2 shows a higher ASA adsorption capacity (2.59 and 1.64 mol·mol^{-1}) after 24 h than other tested adsorbents (0.017 and 0.023 mol·mol^{-1}, Norit@ activated carbon, ASA/adsorbent ratio = 1:0.5 and 1:2, respectively; and 1.87 and 1.06 mol·mol^{-1} MIL-127 ASA/MOF ratio = 1:0.33 and 1.66, respectively).

***In Vivo* Detoxification Efficiency.** The oral detoxification ability of MIL-125-NH_2 was then evaluated *in vivo* during 24 h by administering two different doses of MOF (0.5 and 1 g·kg^{-1}) after 30 min of an ASA overdose (350 mg·kg^{-1}; Supporting Information Section S5). The ASA overdose corresponds to more than 10 times the safe one, which might be enough to determine the detoxification efficiency of MIL-125-NH_2 without causing euthanasia and/or distress of the animal. Concerning MOF doses and for comparison purposes, we selected the same dose as previously reported of MIL-127[19] (1 g·kg^{-1}; ASA@MIL-125-NH_2b group) and half of this dose (0.5 g·kg^{-1}; ASA@MIL-125-NH_2a group), with the aim to investigate the effect of the MOF concentration in the detoxification process. First, to assess the ability of MIL-125-NH_2 to avoid the GI absorption of ASA with time, the salicylate concentration in serum and urine was determined by HPLC after different times (1, 4, 8, and 24 h). Remarkably, except for the first hour after the administration, the salicylate concentration in serum is significantly reduced (up to twofold) in the presence of MIL-125-NH_2a (Figure 2, Table S3),

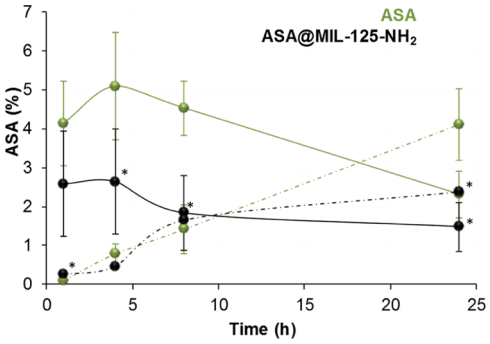

Figure 2. Evolution of ASA concentration with time in serum (solid line) and urine (dotted line) of ASA and ASA@MIL-125-NH_2 groups. ASA levels are reduced twofold in the presence of MIL-125-NH_2. The detoxifying effect of MIL-125-NH_2, once the drug serum peak concentration is reached after 4 h, * indicates a significant change compared to the respective controls ($p < 0.05$) using a two-way Analysis of Variance (ANOVA) test.

indicating that the MOF is able to prevent the salicylate GI absorption. The salicylate absorption seems not to be affected after 1 h, suggesting a poor effect of the MOF in the stomach (in agreement with previous *in vitro* kinetics results; Figure 1), but an important detoxification effect in the gut (4–24 h). Similarly, the salicylate removal by urine is significantly reduced after 24 h in the presence of MIL-125-NH_2, in agreement with a lower toxin absorption.

When compared with Norit@activated carbon (Figures 1 and S7) where 50% of ASA adsorption is reached after 1 h (stomach) but subsequently release (−12% after 2.5 h in intestine), one can consider that the combination of MIL-125-NH_2 and AC could lead to the best performing detoxifying agent. Further direct comparison with the ASA-MIL-127 detoxification is limited by the absence of a kinetic analysis in that study. Only a partial comparison at a single time-point (24 h) is possible, observing that the ASA detoxification using MIL-127 (1 g·kg^{-1}) is within the same range as half dose (0.5 g·kg^{-1}) of MIL-125-NH_2a (0.07 ± 0.04 vs 0.08 ± 0.03 mg·mL^{-1}, respectively).[19]

On the other side, the effect of the MIL-125-NH_2 dose on the ASA detoxification efficacy was evaluated. Interestingly, the salicylates serum concentrations showed no significant differences regardless of the dose of MIL-125-NH_2. This fact might be considered as an advantage regarding the amount of administered MOF to patients, as a high therapeutic index is associated with a favorable safety and efficacy profile.[41] Therefore, we selected the lower MOF dose (ASA@MIL-125-NH_2a group, from now on named ASA@MIL-125-NH_2) to further study its *in vivo* protective effect, safety, and biodistribution.

Oral Overdose Protective Effect and Biosafety. To address the benefit–risk balance of MIL-125-NH_2 in ASA overdose treatment, different parameters (animal behavior, body and organ weight variation, ligand and Ti GI absorption, and biodistribution) were evaluated. First, no behavioral changes or significant differences in body or organ weight were noted in any of the groups (Figure S9). The macroscopic aspect of the organs was totally normal, without hypertrophy, cell necrosis, or color change.

The microscopic examination of stomach, duodenum, jejunum, and ileum showed an important protective effect of MIL-125-NH_2 against deleterious effects associated with ASA overdose (Figure 3, Supporting Information Section S6). Thus,

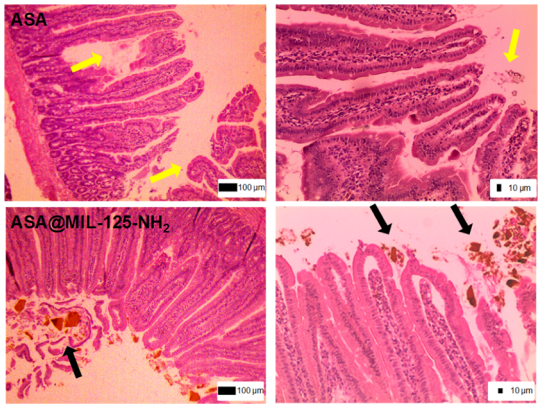

Figure 3. Histological sections of rat duodenum after 24 h of ASA (positive control) and ASA@MIL-125-NH_2 administration. Arrows indicate cellular squamation and necrosis (yellow), MIL-125-NH_2 particles (black).

a histopathological examination of the stomach of the ASA group evidenced significant toxicity, highlighted by the formation of mucosal erosions with cellular desquamation and necrosis of the foveolar mucosal epithelium (Figure S10, yellow arrows). Thus, the exposure to acid of the stomach mucosa is associated with significant damage, including the formation of ulcers, as previously reported.[42] In contrast,

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stomach histological sections of ASA and MIL-125-NH_2-treated animals revealed a normal architecture free from any pathological changes. This finding confirmed the gastro-protective effect of MIL-125-NH_2 particles, which were observed on the surface of the foveolar epithelium (Figure S10 black arrows). Similar to the stomach observations, ASA overdoses produced important toxicity with focal erosions in the intestinal mucosa, showing extensive damage and abnormalities in the duodenum, jejunum, and ileum structure. In the ASA@MIL-125-NH_2 group, a normal villi aspect was found, with the absence of villi fusion and/or swelling (Figure 3, Supporting Information Section S6, red arrows), with no destruction of the enterocyte surface and brush border, supporting again the GI protective effect of the MIL-125-NH_2 detoxifying agent.[43] Further, a significant amount of MIL-125-NH_2 particles were visible around the intestinal microvilli, which might prevent intestinal absorption of salicylates (Figure 3, and Supporting Information Section S6, black arrows). This is particularly important as the vast majority of drug absorption, and in particular aspirin, occurs at the small intestine.[44] Thus, the location of MOF particles around the intestinal microvilli, together with the absence of drug leaching in the bypass to intestinal conditions, makes MIL-125-NH_2 a good detoxifying agent. Additionally, the integrity of MIL-125-NH_2 along the GI tract was evaluated by powder X-ray diffraction (PXRD) of the recovered GI contents and feces. Despite the quite aggressive GI conditions, MIL-125-NH_2 possesses a remarkably high stability, retaining its crystalline structure all along the GI tract after 24 h (Figure 4).

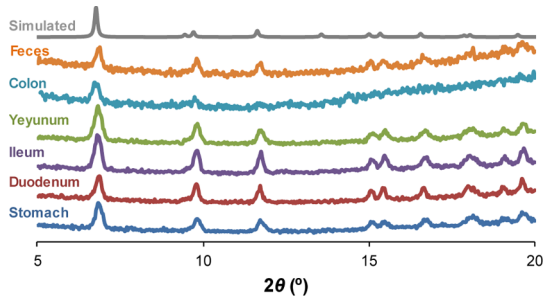

Figure 4. PXRD patterns of the recovered material during passage through the entire GI tract, showing that MIL-125-NH_2 remains stable along the GI tract.

Oral Biodistribution. Finally, we also investigated the oral *in vivo* fate of the MOF, which is a critical point for its future application. Biodistribution of MIL-125-NH_2 was investigated over 24 h by quantifying both titanium and ligand concentration in organs generally involved in the removal of nanoparticulate systems (liver, spleen, kidneys), in serum, and in the GI content, as well as in urine and feces to evaluate its body removal (Supporting Information Section S5). Ti level was quantified by inductively coupled plasma atomic emission spectroscopy (ICP-OES), whereas the linker concentration was determined by specific extraction and HPLC methods (using an adapted method from those previously reported,[45] see the Supporting Information). Considering that MIL-125-NH_2 particle size (ca. 240 nm) is smaller than the maximum size absorbed by the intestinal mucosa (<20 μm),[46] its intestinal crossing could be possible.

Regarding the serum, although the Ti concentration was under the limit of detection (LOD, <0.009 mg·L^{-1}) during the entire kinetic study, an initial maximum absorption of H_2BDC-NH_2 was found in the serum (<0.02% of the administered dose after 1 h). This low ligand amount rapidly decreased up to negligible values at 8 h after administration (Figure S8, Table S4), as a consequence of its direct urinary removal (without metabolism, as confirmed by the detection of the intact ligand in urine). Thus, the poorly absorbed ligand was fast and progressively eliminated in urine up to a maximum value, corresponding to the total removal from serum, avoiding potential deleterious effects by its body accumulation.

Remarkably, the absorption of Ti and ligand (found in serum, liver, spleen, kidneys, and urine) follows different kinetics, reaching the maximum total values of 0.03% (Ti) and 1.05% (H_2BDC-NH_2) of the initial dose after 8 and 24 h, respectively (Figure S8). This finding suggests that the MOF particles are not gastrointestinally absorbed but their free constituents, which is also in agreement with the previously shown MOF partial degradation under gastric conditions (Figure 1). Further, the very low detected concentrations of both, Ti and H_2BDC-NH_2 ligand, confirms their low GI bypass. Even more, from the low amount of absorbed linker (total found in serum and organs = 1.05% of the administered dose), 95% was quickly removed by urine. Thus, only 0.03 and 0.02% of the administered dose was found respectively in spleen and liver after 24 h, not being detectable (<LOD) in the kidneys.

Monitoring the Ti biodistribution over time, one observes an extremely low total Ti GI absorption (0.03% of the administered dose after 8 h), in agreement with its previously reported poor absorption.[21,47] Interestingly, the Ti concentration was reduced thrice at longer times (24 h), as a consequence of its urinary bioelimination (0.02% of the administered dose is removed at 8 h). This observation supports an easy removal of Ti, preventing its accumulation and then, its potentially associated toxicity.

Finally, in the GI content and feces, we found respectively 21 ± 14% and 45 ± 19% of the MIL-125-NH_2 administered dose. It has to be pointed here that some MIL-125-NH_2 remained adhered to the organ surface, as macro- and microscopically observed (specifically in the stomach, Figure S10). Therefore, most of the administered dose remains in the GI tract, resulting in a remarkable GI protection, and being excreted from the body by feces.

Taken as a whole, these results support the oral integrity and safety of the MIL-125-NH_2, exhibiting an important protective effect against the toxicity of ASA overdose.

CONCLUSIONS

We present here for the first time a complete evaluation (safety and biodistribution) of an orally administered Ti-nanoMOF (MIL-125-NH_2) as a novel treatment. Among the tested benchmarked MOFs, the highly GI robust MIL-125-NH_2 is the only MOF able to resist intestinal conditions. Except for a minor absorption, the MOF remains in the GI tract, being directly excreted from the body by feces.

Further, MIL-125-NH_2 is a promising detoxifying agent, able to reduce twofold the salicylate concentration peak in blood, even using a low MOF dose. Moreover, compared to other tested adsorbents (currently used AC and other MOFs), MIL-125-NH_2 is the only material able to adsorb and retain ASA under intestinal conditions, whereas keeping intact their structure and proving a biosafe character and remarkable protective effect against the ASA toxicity. Taking into account

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the efficient toxin encapsulation capacity of AC and MIL-125-NH_2 in the stomach and intestine, respectively, these results pave the way for developing best performing combined detoxifying treatments. These results highlight the potential of Ti-based MOF, and particularly MIL-125-NH_2, as an efficient ASA oral detoxifying agent, with prospects in other toxin or drug intoxications (antidepressants, sedatives, pesticides, etc.) or as a safe oral drug delivery agent.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsami.9b06472.

Synthetic procedures, biological simulated media, stability studies (PXRD and N_2 sorption measurement), HPLC determinations, *in vitro* tests, and *in vivo* biodistribution studies (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Li, H.; Eddaoudi, M.; O'Keeffe, M.; Yaghi, O. M. Design and Synthesis of an Exceptionally Stable and Highly Porous Metal-Organic Frameworks. *Nature* **1999**, *402*, 276−279.

(2) Liu, J.; Chen, L.; Cui, H.; Zhang, J.; Zhang, L.; Su, C.-Y. Applications of Metal-Organic Frameworks in Heterogeneous Supramolecular Catalysis. *Chem. Soc. Rev.* **2014**, *43*, 6011−6061.

(3) Trickett, C. A.; Helal, A.; Al-Maythalony, B. A.; Yamani, Z. H.; Cordova, K. E.; Yaghi, O. M. The Chemistry of Metal-Organic Frameworks for CO_2 Capture, Regeneration and Conversion. *Nat. Rev. Mater.* **2017**, *2*, 1−16.

(4) Giménez-Marqués, M.; Hidalgo, T.; Serre, C.; Horcajada, P. Nanostructured Metal−organic Frameworks and Their Bio-Related Applications. *Coord. Chem. Rev.* **2016**, *307*, 342−360.

(5) Simón-Yarza, T.; Mielcarek, A.; Couvreur, P.; Serre, C. Nanoparticles of Metal-Organic Frameworks: On the Road to In Vivo Efficacy in Biomedicine. *Adv. Mater.* **2018**, *30*, 1707365.

(6) Doonan, C.; Riccò, R.; Liang, K.; Bradshaw, D.; Falcaro, P. Metal-Organic Frameworks at the Biointerface: Synthetic Strategies and Applications. *Acc. Chem. Res.* **2017**, *50*, 1423−1432.

(7) Lucena, F. R. S.; de Araújo, L. C. C.; Rodrigues, M. d. D.; da Silva, T. G.; Pereira, V. R. A.; Militão, G. C. G.; Fontes, D. A. F.; Rolim-Neto, P. J.; da Silva, F. F.; Nascimento, S. C. Induction of Cancer Cell Death by Apoptosis and Slow Release of 5-Fluoracil from Metal-Organic Frameworks Cu-BTC. *Biomed. Pharmacother.* **2013**, *67*, 707−713.

(8) Hartlieb, K. J.; Ferris, D. P.; Holcroft, J. M.; Kandela, I.; Stern, C. L.; Nassar, M. S.; Botros, Y. Y.; Stoddart, J. F. Encapsulation of Ibuprofen in CD-MOF and Related Bioavailability Studies. *Mol. Pharm.* **2017**, *14*, 1831−1839.

(9) Shih, Y.-H.; Kuo, Y.-C.; Lirio, S.; Wang, K.-Y.; Lin, C.-H.; Huang, H.-Y. A Simple Approach to Enhance the Water Stability of a Metal-Organic Framework. *Chem.—Eur. J.* **2017**, *23*, 42−46.

(10) Singh, V.; Guo, T.; Xu, H.; Wu, L.; Gu, J.; Wu, C.; Gref, R.; Zhang, J. Moisture Resistant and Biofriendly CD-MOF Nanoparticles Obtained: Via Cholesterol Shielding. *Chem. Commun.* **2017**, *53*, 9246−9249.

(11) Howell, B. A.; Chauhan, A. Current and Emerging Detoxification Therapies for Critical Care. *Materials* **2010**, *3*, 2483−2505.

(12) https://wonder.cdc.gov/, accessed 01/05/19.

(13) http://www.emcdda.europa.eu/publications/edr/trends-developments/2017, accessed 01/05/19.

(14) Bae, H.; Lee, K. Medico-legal Consideration of Gastric Lavage in Acutely Intoxicated Patients. *Emerg. Med. J.* **2007**, *24*, 233.

(15) Graham, L. M.; Nguyen, T. M.; Lee, S. B. Nanodetoxification: Emerging Role of Nanomaterials in Drug Intoxication Treatment. *Nanomedicine* **2011**, *6*, 921−928.

(16) Watson, W. A.; Cremer, K. F.; Chapman, J. A. Gastrointestinal Obstruction Associated With Multiple-Dose Activated Charcoal. *J. Emerg. Med.* **1986**, *4*, 401−407.

(17) Neuvonen, P. J.; Olkkola, K. T. Oral Activated Charcoal in the Treatment of Intoxications. *Med. Toxicol. Adverse Drug Exp.* **1988**, *3*, 33−58.

(18) Albertson, T. E.; Owen, K. P.; Sutter, M. E.; Chan, A. L. Gastrointestinal Decontamination in the Acutely Poisoned Patient. *Int. J. Emerg. Med.* **2011**, *4*, 65.

(19) Rojas, S.; Baati, T.; Njim, L.; Manchego, L.; Neffati, F.; Abdeljelil, N.; Saguem, S.; Serre, C.; Najjar, M. F.; Zakhama, A.; Horcajada, P. Metal-Organic Frameworks as Efficient Oral Detoxifying Agents. *J. Am. Chem. Soc.* **2018**, *140*, 9581−9586.

(20) Horcajada, P.; Serre, C.; Vallet-Regí, M.; Sebban, M.; Taulelle, F.; Férey, G. Metal-Organic Frameworks as Efficient Materials for Drug Delivery. *Angew. Chem., Int. Ed.* **2006**, *45*, 5974−5978.

(21) Cho, W.-S.; Kang, B.-C.; Lee, J. K.; Jeong, J.; Che, J.-H.; Seok, S. H. Comparative Absorption, Distribution, and Excretion of Titanium Dioxide and Zinc Oxide Nanoparticles after Repeated Oral Administration. *Part. Fibre Toxicol.* **2013**, *10*, , 9. DOI: 10.1186/1743-8977-10-9

(22) Dan-Hardi, M.; Serre, C.; Frot, T.; Rozes, L.; Maurin, G.; Sanchez, C.; Férey, G. A New Photoactive Highly Porous Titanium (IV) Dicarboxylate. *J. Am. Chem. Soc.* **2009**, *131*, 10857−10859.

(23) Vilela, S.; Salcedo-Abraira, P.; Colinet, I.; Salles, F.; De Koning, M.; Joosen, M.; Serre, C.; Horcajada, P. Nanometric MIL-125-NH_2 Metal−Organic Framework as a Potential Nerve Agent Antidote Carrier. *Nanomaterials* **2017**, *7*, 321−336.

(24) 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*, 2994−3003.

(25) Decker, W.; Corby, D. G.; Ibanez, J. D. Aspirin Adsorption with Activated Charcoal. *Lancet* **1968**, *291*, 754−755.

(26) Mund, M. E.; Gyo, C.; Brüggmann, D.; Quarcoo, D.; Groneberg, D. A. Acetylsalicylic Acid as a Potential Pediatric Health Hazard: Legislative Aspects Concerning Accidental Intoxications in the European Union. *J. Occup. Med. Toxicol.* **2016**, *11*, 32.

(27) Michael, J. B.; Sztajnkrycer, M. D. Deadly Pediatric Poisons: Nine Common Agents That Kill at Low Doses. *Emerg. Med. Clin. N. Am.* **2004**, *22*, 1019−1050.

(28) Suzanne Schoenfelt, M.-M. E. *Comprehensive Advanced Life Support*; CALS, 2011.

(29) Danel, V.; Henry, J. A. Activated Charcoal , Emesis , and Gastric Lavage in Aspirin Overdose. *Br. Med. J.* **1988**, *296*, 1507.

(30) Glucksman, D. H. *Biomembranes*, 1st ed.; Springer: Sheffield, 1974.
(31) Horcajada, P.; Chalati, T.; Serre, C.; Gillet, B.; Sebrie, C.; Baati, T.; Eubank, J. F.; Heurtaux, D.; Clayette, P.; Kreuz, C.; Chang, J.-S.; Hwang, Y. K.; Marsaud, V.; Bories, P.-N.; Cynober, L.; Gil, S.; Férey, G.; Couvreur, P.; Gref, R. Porous Metal-Organic-Framework Nanoscale Carriers as a Potential Platform for Drug Delivery and Imaging. *Nat. Mater.* **2010**, *9*, 172−178.
(32) Devic, T.; Horcajada, P.; Serre, C.; Salles, F.; Maurin, G.; Moulin, B.; Heurtaux, D.; Clet, G.; Vimont, A.; Grenèche, J.-M.; Ouay, F.B. L.; Moreau, F.; Magnier, E.; Filinchuk, Y.; Marrot, J.; Lavalley, J.-C.; Daturi, M. Functionalization in Flexible Porous Solids: Effects on the Pore Opening and the Host-Guest Interactions. *J. Am. Chem. Soc.* **2010**, *132*, 1127−1136.
(33) Canioni, R.; Roch-Marchal, C.; Sécheresse, F.; Horcajada, P.; Serre, C.; Hardi-Dan, M.; Férey, G.; Grenèche, J.-M.; Lefebvre, F.; Chang, J.-S.; Hwang, Y.-K.; Lebedev, O.; Turner, S.; Van Tendeloo, G. Stable Polyoxometalate Insertion within the Mesoporous Metal Organic Framework MIL-100(Fe). *J. Mater. Chem.* **2011**, *21*, 1226.
(34) Cavka, J. H.; Jakobsen, S.; Olsbye, U.; Guillou, N.; Lamberti, C.; Bordiga, S.; Lillerud, K. P. A New Zirconium Inorganic Building Brick Forming Metal Organic Frameworks with Exceptional Stability. *J. Am. Chem. Soc.* **2008**, *130*, 13850−13851.
(35) Kandiah, M.; Nilsen, M. H.; Usseglio, S.; Jakobsen, S.; Olsbye, U.; Tilset, M.; Larabi, C.; Quadrelli, E. A.; Bonino, F.; Lillerud, K. P.; Lyon, D. Synthesis and Stability of Tagged UiO-66 Zr-MOFs. *Chem. Mater.* **2010**, *22*, 6632−6640.
(36) Kida, K.; Okita, M.; Fujita, K.; Tanaka, S.; Miyake, Y. Formation of High Crystalline ZIF-8 in an Aqueous Solution. *CrystEngComm* **2013**, *15*, 1794−1801.
(37) Sellers, E. M.; Khouw, V.; Dolman, L. Comparative Drug Adsorption by Activated Charcoal. *J. Pharm. Sci.* **1977**, *66*, 1640−1641.
(38) Frenia, M. L.; Schauben, J. L.; Wears, R. L.; Karlix, J. L.; Tucker, C. A.; Kunisaki, T. A. Multiple-Dose Activated Charcoal Compared to Urinary Alkalinization for the Enhancement of Phenobarbital Elimination. *J. Toxicol. Clin. Toxicol.* **1996**, *34*, 169−175.
(39) Brahmi, N.; Kouraichi, N.; Thabet, H.; Amamou, M. Influence of Activated Charcoal on the Pharmacokinetics and the Clinical Features of Carbamazepine Poisoning. *Am. J. Emerg. Med.* **2006**, *24*, 440−443.
(40) Chyka, P. A.; Erdman, A. R.; Christianson, G.; Wax, P. M.; Booze, L. L.; Manoguerra, A. S.; Martin Caravati, E.; Nelson, L. S.; Olson, K. R.; Cobaugh, D. J.; Scharman, E. J.; Woolf, A. D.; Troutman, W. G. Salicylate Poisoning: An Evidence-Based Consensus Guideline for out-of-Hospital Management. *Clin. Toxicol.* **2007**, *45*, 95−131.
(41) Junutula, J. R.; Raab, H.; Clark, S.; Bhakta, S.; Leipold, D. D.; Weir, S.; Chen, Y.; Simpson, M.; Tsai, S. P.; Dennis, M. S.; Lu, Y.; Meng, Y. G.; Ng, C.; Yang, J.; Lee, C. C.; Duenas, E.; Gorrell, J.; Katta, V.; Kim, A.; McDorman, K.; Flagella, K.; Venook, R.; Ross, S.; Spencer, S. D.; Lee Wong, W.; Lowman, H. B.; Vandlen, R.; Sliwkowski, M. X.; Scheller, R. H.; Polakis, P.; Mallet, W. Site-Specific Conjugation of a Cytotoxic Drug to an Antibody Improves the Therapeutic Index. *Nat. Biotechnol.* **2008**, *26*, 925−932.
(42) Wang, Z.; Hasegawa, J.; Wang, X.; Matsuda, A.; Tokuda, T.; Miura, N.; Watanabe, T. Protective Effects of Ginger against Aspirin-Induced Gastric Ulcers in Rats. *Yonago Acta Med.* **2011**, *54*, 11−9.
(43) Rose, J. Digestion and the Structure and Function of the Gut. *J. Anat.* **1987**, *8*, 151−260.
(44) Ascjenbrenner, D. S.; Venable, S. *J. Drug Therapy in Nursing*; 2009.
(45) Simon-Yarza, T.; Baati, T.; Neffati, F.; Njim, L.; Couvreur, P.; Serre, C.; Gref, R.; Najjar, M. F.; Zakhama, A.; Horcajada, P. In vivo Behavior of MIL-100 Nanoparticles at Early Times after Intravenous Administration. *Int. J. Pharm.* **2016**, *511*, 1042−1047.
(46) Patel, J.; Patel, A. Toxicity of Nanomaterials on the Liver, Kidney, and Spleen. In *Biointeractions of Nanomaterials*; Taylor & Francis Group, 2015; pp 286−306.
(47) Geraets, L.; Oomen, A. G.; Krystek, P.; Jacobsen, N. R.; Wallin, H.; Laurentie, M.; Verharen, H. W.; Brandon, E. F. A.; de Jong, W. H. Tissue Distribution and Elimination after Oral and Intravenous Administration of Different Titanium Dioxide Nanoparticles in Rats. *Part. Fibre Toxicol.* **2014**, *11*, 1−21.

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