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Ti-Based nanoMOF as an Efficient Oral Therapeutic Agent

Sara Rojas,^{†,‡} Nathalie Guillou,[‡] and Patricia Horcajada^{*,†}

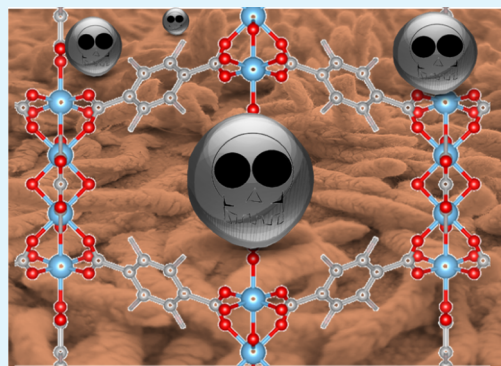
[†]IMDEA Energy, Av. Ramón de la Sagra 3, 28935 Móstoles-Madrid, Spain

[‡]Institut Lavoisier, CNRS UMR 8180, UVSQ, Université Paris-Saclay, 45, Avenue Des Etats Unis, 78035 Versailles Cedex, France

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) aminoterephthalate MIL-125-NH₂ or Ti₈O₈(OH)₄(O₂C-C₆H₃NH₂-CO₂)₆ as the nanoMOF, exhibiting several features that make it an excellent oral detoxifying candidate: (i) it is based on Ti (oral lethal dose LD₅₀ = 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 ($S_{\text{BET}} \approx 1400 \text{ m}^2\cdot\text{g}^{-1}$, $V_p \approx 0.6 \text{ cm}^3\cdot\text{g}^{-1}$ with octahedral $\sim 12.5 \text{ \AA}$ and tetrahedral cavities $\sim 6 \text{ \AA}$, accessible via windows $\sim 5\text{--}7 \text{ \AA}$), which provides structural superiority for the encapsulation of drugs;²² and (iv) it can be synthesized at the nanoscale (discs of $390 \pm 94 \times 241 \pm 65 \text{ nm}$, $n = 150$), 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 $7.8 \times 5.8 \times 2.3 \text{ \AA}$ calculated by density functional theory).²⁴ Although used as a model in this study, allowing an easy comparison with previously reported adsorbents²⁵ (including the novel MOF adsorbent),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 ($150 \text{ mg}\cdot\text{kg}^{-1}$; 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-NH₂ 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-NH₂ keeps its crystalline structure and microporosity 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

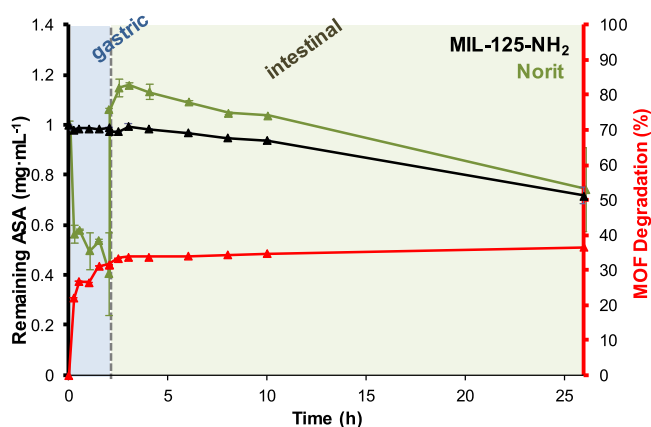


Figure 1. Comparative evolution of salicylate removal using MIL-125-NH₂ (left, black) and Norit@AC (left, green) using the same amount (mass) of adsorbent and the same ASA initial concentration under simulated GI conditions (the blue and green backgrounds represent gastric and intestinal media, respectively). The concentrations of salicylates have been normalized for an easier comparison. The MIL-125-NH₂ 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)-NH₂,³⁵ 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-NH₂), 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-NH₂ occurs under gastric conditions ($\sim 30\%$, Figure 1), this solid is able to resist the GI harsh environment (total degradation $\sim 35\%$), 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-NH₂ is the only MOF able to retain and adsorb ASA under intestinal conditions.

After 24 h, MIL-125-NH₂ 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

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-NH₂ 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-NH₂ material is the best performing ASA detoxifying agent. In terms of drug loading capacity, MIL-125-NH₂ 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-NH₂ 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-NH₂ 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-127¹⁹ (1 g·kg⁻¹; ASA@MIL-125-NH₂b group) and half of this dose (0.5 g·kg⁻¹; ASA@MIL-125-NH₂a group), with the aim to investigate the effect of the MOF concentration in the detoxification process. First, to assess the ability of MIL-125-NH₂ 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-NH₂a (Figure 2, Table S3),

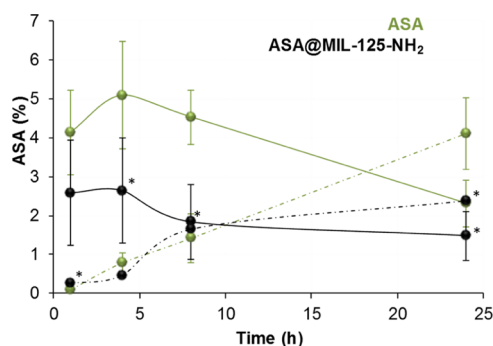


Figure 2. Evolution of ASA concentration with time in serum (solid line) and urine (dotted line) of ASA and ASA@MIL-125-NH₂ groups. ASA levels are reduced twofold in the presence of MIL-125-NH₂. The detoxifying effect of MIL-125-NH₂ once the drug serum peak concentration is reached after 4 h, * indicates 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-NH₂, 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-NH₂ 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-NH₂a (0.07 ± 0.04 vs 0.08 ± 0.03 mg·mL⁻¹, respectively).¹⁹

On the other side, the effect of the MIL-125-NH₂ dose on the ASA detoxification efficacy was evaluated. Interestingly, the salicylates serum concentrations showed no significant differences regardless of the dose of MIL-125-NH₂. 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-NH₂a group, from now on named ASA@MIL-125-NH₂) 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-NH₂ 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-NH₂ against deleterious effects associated with ASA overdose (Figure 3, Supporting Information Section S6). Thus,

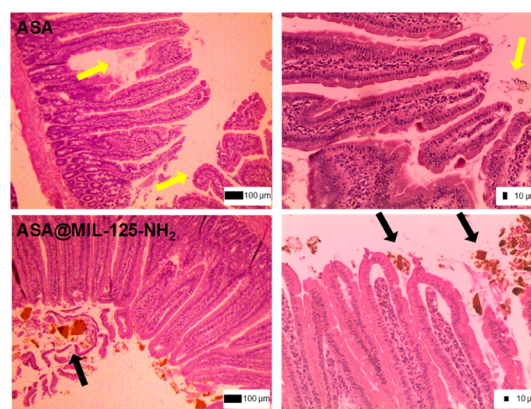


Figure 3. Histological sections of rat duodenum after 24 h of ASA (positive control) and ASA@MIL-125-NH₂ administration. Arrows indicate cellular squamation and necrosis (yellow), MIL-125-NH₂ particles (black).

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,

stomach histological sections of ASA and MIL-125-NH₂-treated animals revealed a normal architecture free from any pathological changes. This finding confirmed the gastro-protective effect of MIL-125-NH₂ 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-NH₂ 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-NH₂ detoxifying agent.⁴³ Further, a significant amount of MIL-125-NH₂ 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-NH₂ a good detoxifying agent. Additionally, the integrity of MIL-125-NH₂ 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-NH₂ possesses a remarkably high stability, retaining its crystalline structure all along the GI tract after 24 h (Figure 4).

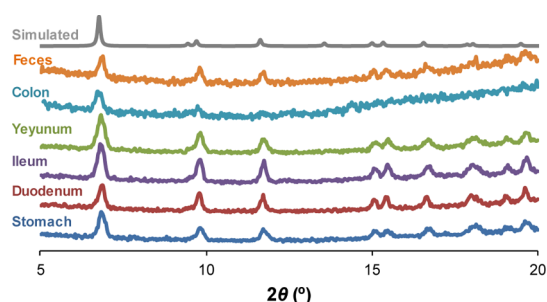


Figure 4. PXRD patterns of the recovered material during passage through the entire GI tract, showing that MIL-125-NH₂ remains stable along the GI tract.

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-NH₂ 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-NH₂ 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 H₂BDC-NH₂ 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% (H₂BDC-NH₂) 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 H₂BDC-NH₂ 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-NH₂ administered dose. It has to be pointed here that some MIL-125-NH₂ 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-NH₂, 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-NH₂) as a novel treatment. Among the tested benchmarked MOFs, the highly GI robust MIL-125-NH₂ 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-NH₂ 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-NH₂ 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

the efficient toxin encapsulation capacity of AC and MIL-125-NH₂ 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-NH₂, 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 N₂ sorption measurement), HPLC determinations, *in vitro* tests, and *in vivo* biodistribution studies (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: patricia.horcajada@imdea.org.

ORCID

Sara Rojas: 0000-0002-7874-2122

Patricia Horcajada: 0000-0002-6544-5911

Notes

The authors declare no competing financial interest.

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