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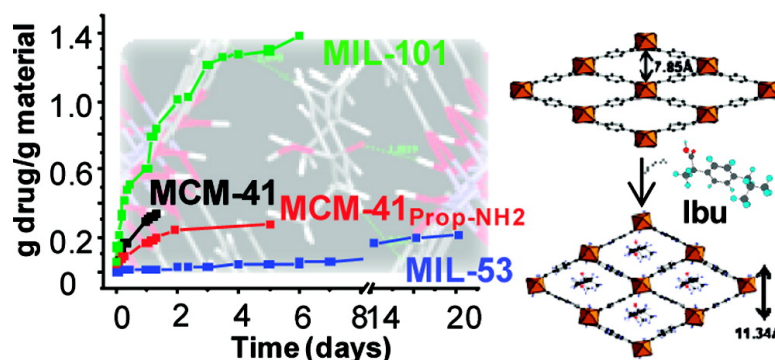
Flexible Porous Metal-Organic Frameworks for a Controlled Drug Delivery

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Flexible Porous Metal-Organic Frameworks for a Controlled Drug Delivery

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Abstract: Flexible nanoporous chromium or iron terephtalates (BDC) MIL-53(Cr, Fe) or M(OH)[BDC] have been used as matrices for the adsorption and in vitro drug delivery of Ibuprofen (or α-*p*-isobutylphenyl-propionic acid). Both MIL-53(Cr) and MIL-53(Fe) solids adsorb around 20 wt % of Ibuprofen (Ibuprofen/dehydrated MIL-53 molar ratio = 0.22(1)), indicating that the amount of inserted drug does not depend on the metal (Cr, Fe) constitutive of the hybrid framework. Structural and spectroscopic characterizations are provided for the solid filled with Ibuprofen. In each case, the very slow and complete delivery of Ibuprofen was achieved under physiological conditions after 3 weeks with a predictable zero-order kinetics, which highlights the unique properties of flexible hybrid solids for adapting their pore opening to optimize the drug-matrix interactions.

Introduction

The synthesis of new bioactive compounds of very high molecular weight with therapeutic activity and/or with a low aqueous solubility becomes more and more complex and the processes for their commercialization very slow. This requires the use of carrier systems to improve the activity of known molecules. These systems usually allow a better control of the drug plasmatic levels, increasing the efficiency and decreasing the toxicity, as well as an increase in the drug stability by protection of the biodegradation. Until recently, polymeric and mixed systems have been recently proposed for a better controlled release of drugs.[1] In particular, mesoporous inorganic solids such as the ordered mesoporous silicas (pure or functionalized by a postsynthesis modification) are now used.[2] However, this process leads to a decrease of the drug storage capacity.[3]

Recently, an alternative route (the hybrid route) has been proposed using for the first time porous metal-organic frameworks (MOFs) as new controlled delivery systems.[4] These solids combine a high pore volume, a regular porosity, and the presence of tunable organic groups within the framework which allow an easy modulation of the size of the pores. The first example concerned the adsorption of the model molecule Ibuprofen in the *rigid* MOFs MIL-100 and MIL-101 (MIL = Material Institut Lavoisier) with very large pores. They exhibit a very high drug storage capacity, up to an unprecedented 1.4 g of drug per gram of porous solid, and a complete drug controlled release under physiological conditions from 3 to 6 days.

The skeleton of MOFs can sometimes be flexible,[5] and we recently reported a new class of dynamic hybrid solids which modulate their pore size upon adsorption of organic molecules.[6] This reversible "swelling" effect increases the cell volumes of the parent structure by 50−230%, depending on the structure and the length of the linker[6,7] without any apparent bond breaking. It concerned primitively the MIL-53 family which

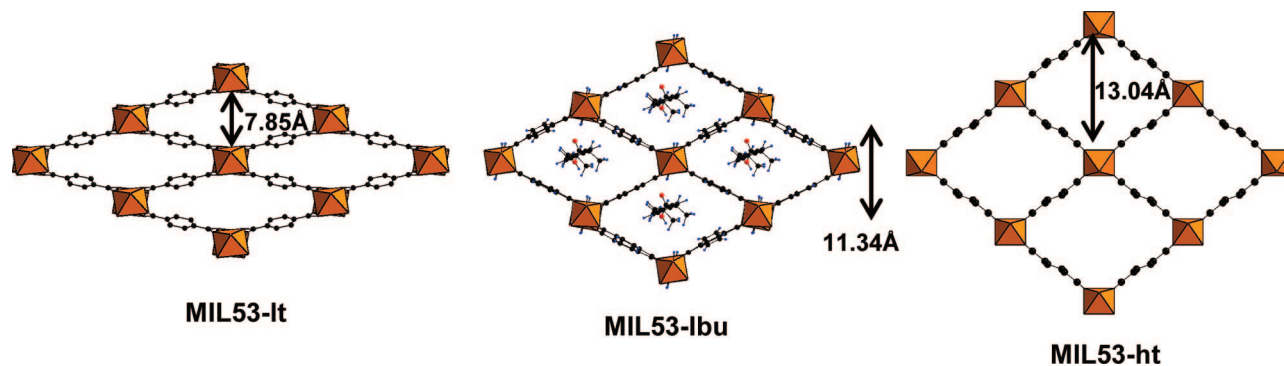† Université de Versailles St-Quentin en Yvelines.
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Figure 1. Schematic 3D representation of the breathing effect of the MIL-53(Cr) hybrid solid upon dehydration−hydration.

breathes in the presence of gases.[8] We therefore aimed at studying the effect of this breathing phenomenon on the drug adsorption and delivery properties of pharmacological molecules. Once more, Ibuprofen (hereafter noted Ibu) was chosen as a model molecule for its simple structure, and this paper will look at two points: (i) the influence of breathing on drug adsorption and (ii) the characterizations and the induced effects of the host−drug interactions (including kinetics of delivery in a simulated physiological environment).

Two flexible materials were used: (i) MIL-53(Cr) solid as a model material despite the well-known toxicity of chromium compounds;[9] (ii) the much less toxic iron analogue MIL-53(Fe) (rat oral dose: $DL_{50}(Fe) = 30$ g/kg, $DL_{50}(1,4$-benzene dicarboxylic acid or terephthalic acid; 1,4-BDC) > 6.4 g/kg).[10,11] Complementary Fourier transformed infrared and (^{1}H, ^{13}C) solid state NMR experiments have been performed in order to characterize the drug-matrix interactions as well as the arrangement of Ibuprofen within the pore of the material. These experimental conclusions were then supported by periodic DFT simulations performed on Ibu/MIL-53(Fe).

Results

The porous metal terephthalates MIL-53 solids are built up from terephathalate anions and trans chains of metal(III) octahedra sharing OH groups, creating a three-dimensional framework with a one-dimensional pore channel system ($\varphi \sim$ 8 Å) (Figure 1). Their formulas are $M^{III}(OH) \cdot [O_2C−C_6H_4−CO_2] \cdot H_2O$ ($M^{III} =$ Al, Cr, Fe) for the hydrated forms (MIL-53lt; lt = low temperature) or $M^{III}(OH) \cdot [O_2C−C_6H_4−CO_2]$ for the dehydrated compounds (MIL-53ht; ht = high temperature). The aluminum and chromium MIL-53lt solids exhibit a reversible pore opening which involves atomic displacements by 5.2 Å upon dehydration, while the iron analogue[12,13] opens its pores only during the adsorption of

molecules. For the Al and Cr solids, the structural change upon dehydration−hydration cycles can be explained by the formation of hydrogen bondings between the water molecules and the inorganic hydrophilic parts of the pore.[14]

Adsorption. Adsorption of Ibuprofen was carried out in MIL-53(Cr, Fe) solids by impregnation of the title solids under stirring in Ibuprofen containing hexane solutions. The solids were dehydrated at 150 °C overnight prior to the insertion of the drug in order to avoid the presence of water inside the pores which renders more difficult the adsorption of the hydrophobic Ibuprofen molecules. The Ibuprofen content was estimated by UV−vis spectroscopy, thermogravimetric analysis (TGA), elemental analysis, and X-ray fluorescence (XRF) (see Table S1 and Figure S1 in Supporting Information).

To reach a maximal drug loading, several parameters were tested. Increased temperatures or repeated impregnations did not affect the drug loading capacity. On the contrary, the nature of the solvent, the contact time, and the Ibuprofen to porous solid relative ratio have a major influence on the amount of drug adsorbed (see Table S1 in Supporting Information). On the first point, the final adsorbed Ibuprofen content depends on the relative affinity between the solvent, the Ibuprofen, and the porous internal surface. The amounts of Ibu are larger using nonpolar hexane than polar ethanol as solvents. In the same way, the adsorbed amount of Ibuprofen increases with the initial Ibuprofen/material ratio expressed in weight. The optimal value (3:1) corresponds to the maximum solubility of Ibuprofen in hexane. Finally, the contact time is also important. The maximum of adsorption is obtained only after 3 days (Table S2 and Figure S2 in Supporting Information). Thus, the best results were achieved in both cases (Cr, Fe) when dehydrated solids were soaked for 3 days in a 30 mg·mL^{-1} hexane Ibuprofen-containing solution with an Ibuprofen to material weight ratio of 3:1. Chemical analysis indicates that both MIL-53(Cr) and MIL-53(Fe) solids adsorb around 20 wt % of Ibuprofen (Table 1), which corresponds to an Ibuprofen/M(Cr, Fe) molar ratio = 0.22(1), showing that at least the drug adsorbed amount does not depend on the metal. The influence of the latter will affect other factors (see below). In these conditions, N_2 adsorption isotherms performed after the Ibuprofen incorporation for the MIL-53(Cr)−Ibu system show that there were almost no residual porosity (Figure S6 and Table S4 in Supporting Information). Similar N_2 adsorption measure-

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Table 1. Nitrogen Adsorption Data (77 K, P_0 = 1 atm) and Ibuprofen Content for the Different MIL-53 Materials (The Nitrogen Adsorption Data Are Not Reported for The MIL-53(Fe) As This Material Does Not Present Any Porosity for Nitrogen At 77 K)

		MIL-53ht(Cr)[a]	MIL-53ht(Fe)[a]
starting materials	$S_{Langmuir}$ (m^2·g^{-1})	1500	−
	V_{pore} (cm^3·g^{-1})	0.60	−
IBU materials	$S_{Langmuir}$ (m^2·g^{-1})	84	−
	V_{pore} (cm^3·g^{-1})	0.07	−
	g IBU/g dehydrated material	0.220	0.210
total Ibuprofen release [Ibu] = Kt (mg·g^{-1}·day^{-1})		[Ibu] = −6.245 + 0.465t	[Ibu] = 6.020 + 0.432t
stage 1 (mg·g^{-1}·day^{-1})		[Ibu] = 2.148 + 0.337t (0−10 days)	[Ibu] = 34.179 − 33.848 e$^{(-t/9.674)}$ (0−4 days) exponential
stage 2 (mg·g^{-1}·day^{-1})		[Ibu] = −84.296 + 0.704t (11−21 days)	[Ibu] = −8.067 + 0.478t (5−21 days)

[a] ht: high temperature form.
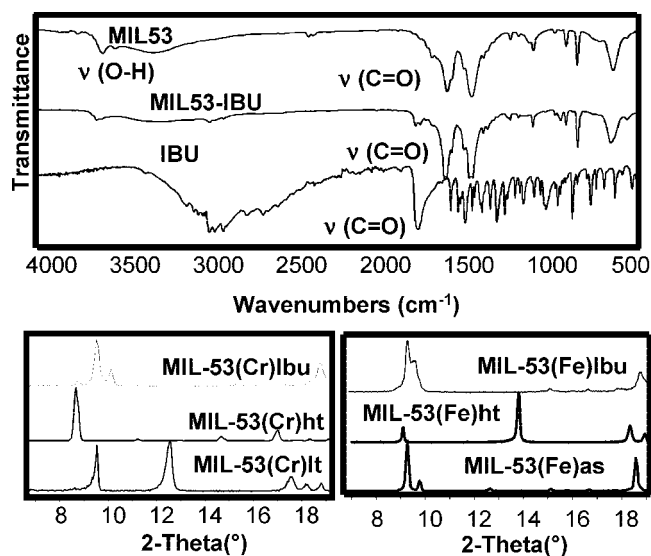
Figure 2. Top: IR spectra of MIL-53(Fe), MIL-53(Fe) loaded with Ibuprofen, Ibuprofen. Bottom: XRPD patterns of MIL-53(Cr and Fe) (λ_{Cu} = 1.5406 Å).

ments were not carried out in MIL-53(Fe) materials since the dehydrated form (closed form) exhibits no porosity for nitrogen at 77 K.

X-ray Diffraction. The breathing effect drastically affects the X-ray powder diffraction (XRPD) patterns of the phases, with changes in the cell volumes and symmetry. From monoclinic (*C2/c*, No. 15) for the less opened form MIL-53(Cr)lt, it becomes orthorhombic for the more opened forms MIL-53(Cr)as (*Pnma*, No. 62) (as: as-synthesized) and MIL-53(Cr)ht (*Imcm*, No. 74). In contrast, as-synthesized and dehydrated MIL-53(Fe) shows a monoclinic symmetry (*C2/c*, No. 15), the channels of anhydrous (MIL-53(Fe)ht; $V \sim 900$ Å^3), staying closed unlike its Cr analogue. They reopen only in the presence of solvent molecules (MIL-53(Fe)as; $V \sim 1393$ Å^3 with DMF).[6,14] In their filled form, the structures of the Cr and Fe solids are identical (see Figures S3 and S4 in Supporting Information).

Figure 2 shows the main peaks position of the XRPD patterns of the Ibuprofen-containing solids (MIL−Ibu). They are located between those of the open and closed structures, indicating a partial pore opening upon incorporation of Ibuprofen into the pores. TGA measurements (Figure S2 in Supporting Information) show that Ibuprofen leaves the pores of MIL-53 at ca. 260 °C. Using a glass capillary, an adequate heating under vacuum and high flux X-ray synchrotron radiation (see Supporting Information) of the Swiss Norvegian Beamline of the ESRF allows complete removal of hexane and isolates the pure Ibuprofen−MIL-53(Fe) solid. The resulting high-quality XRPD

pattern was indexed using Dicvol in a monoclinic cell (space group *C2/c* (No. 15) $V \approx 1400$ Å^3) (see Table 2 and Figure 2), close to those of the DMF (MIL-53(Fe)dmf) solid; this similarity is further confirmed by its thermogravimetric analysis which shows an approximate 20 wt % weight loss of DMF, in agreement with the 20 wt % content of Ibuprofen in the MIL-53(Fe) system.

FTIR and NMR. Fourier transformed infrared spectroscopy (FTIR) confirmed the incorporation of the drug molecule during the adsorption process (Figure 2 and Figure S7 in Supporting Information) with the presence of ν(C−H) at 2900 cm^{-1} and vibrational bands characteristic of the −O−C−O− group around 1550 and 1430 cm^{-1} as well as a typical increase of the intensity of ν(ArC−H) bands at 3050 cm^{-1}. Furthermore, the shift of the ν(C=O) band of the carboxylic group of Ibuprofen from 1695 to 1725 cm^{-1} correlated to those of the vibrational band ν(O−H) of the inorganic chains of MIL-53 from 3656 to 3639 cm^{-1}, indicates the formation of a hydrogen bond between the carboxylic group of Ibuprofen and the hydroxyl group of MIL-53.

In order to deeply analyze the nature of the drug-matrix interactions, ^{1}H and ^{13}C solid state NMR experiments were performed on both the pure constituents (Ibuprofen and MIL-53(Cr)) and MIL-53(Cr)−Ibu (Figure 3 and Figures S12 and S13 in Supporting Information). ^{1}H NMR spectrum shows that the Ibuprofen molecule in MIL-53(Cr) is in its neutral form. Compared to the spectrum for the pure Ibuprofen, lines are broadened, due to the paramagnetic effect of the chromium atoms. The spectrum of MIL-53(Cr)−Ibu displays many spinning side bands. So, the apparent chemical shift anisotropy of the ^{1}H NMR spectrum reflects a fraction of the **g**-tensor of the paramagnetic electrons transferred to the ^{1}H nucleus through the electron−nuclear dipolar coupling. At first sight, the interactions between Ibuprofen molecules and MIL-53(Cr) seem strong (Figure S12 in Supporting Information), which would be consistent with the interaction energy calculated for the Ibuprofen/MIL-53(Fe) system by our DFT approach (see below). The ^{13}C NMR spectra of MIL-53(Cr)−Ibu show a broadening of the signal due not only to the paramagnetic effect of chromium atoms but also to a distribution of chemical shifts, which can be related to a conformational distribution of the drug in the cavities of MIL-53(Cr) or/and to an increase of the Ibuprofen mobility. This effect concerns essentially the aromatic part of Ibuprofen. In addition, the ^{13}C CPMAS NMR spectra of MIL-53(Cr)−Ibu and MIL-53(Fe)−Ibu are very close to those obtained for the pure Ibuprofen, revealing that Ibuprofen in MIL-53(Cr) exhibits a conformation close to that of its pure form (Figure S13 in Supporting Information). This observation was also confirmed by our DFT optimized geometry (Figure 4).

Table 2. Estimated Cell Parameters for MIL-53(Fe) Inserting Different Moieties (Space Groups are *C2/c* (No. 15) Except for the DMC Form (*Imcm*, No. 74)

solid	a (Å)	b (Å)	c (Å)	β (°)	cell volume (Å³)	solvent content (%)
MIL-53(Fe), dry	21.25(1)	6.76(1)	6.88(1)	114.6(1)	899.1(1)	
MIL-53(Fe)H₂O	21.08(1)	7.62(1)	6.81(1)	114.90(2)	992.1(1)	6.7
MIL-53(Fe)−Ibu	19.23(1)	11.34(1)	6.90(1)	110.82(2)	1406.7(3)	20
MIL-53(Fe)dmf	19.05(1)	11.27(1)	6.86(1)	108.9(1)	1392.6(1)	20
MIL-53(Fe)dmc[a]	15.89(1)	14.44(1)	6.89(1)	90	1580.0(1)	n.a.

[a] dmc: dimethylcarbonate; dmf: dimethylformamide; Ibu = Ibuprofen; n.a.: not available.
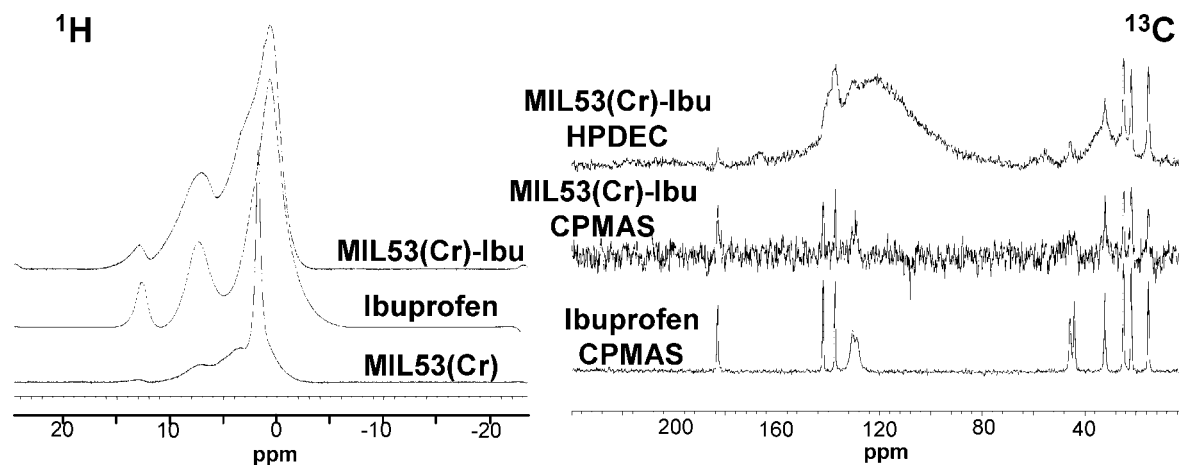
Figure 3. ¹H and ¹³C NMR spectra of MIL-53(Cr) loaded with Ibuprofen, Ibuprofen, MIL-53(Cr).

DFT Simulations. Using the cell parameters deduced from the XRPD pattern, periodic DFT calculations were then performed on MIL-53(Fe)–Ibu (see Supporting Information for details) to localize the drug molecules. Figure 4 reports the DFT optimized geometry obtained for one Ibuprofen molecule per pore of MIL-53(Fe), which roughly corresponds to the experimental uptake. It shows that the most likely interaction involves a strong hydrogen bonding between the oxygen of the carboxylic group of Ibuprofen and the hydroxyl group of the matrix, located at the surface of the MIL-53(Fe) material with a characteristic $O_{(COOH)}-H_{(\mu 2\text{-}OH)}$ distance of 1.80 Å. In addition, weaker van der Waals and/or CH−π interactions are found between the hydroxyl and the methyl groups of the Ibuprofen molecule and the organic linker of MIL-53(Fe). In agreement with the ¹³C CPMAS NMR data, the spatial geometry of the Ibuprofen molecule within the pore of the MIL-53(Fe) is slightly modified compared to those obtained by an optimization of the single molecule in the gas phase (Figure 4). Only some rotations of elements of the Ibuprofen structure are observed.

This optimized geometry leads to a high drug-matrix interaction energy of 57 kJ·mol⁻¹, which is higher than those previously observed for the quadrupolar CO_2 molecule interacting with the MIL-53(Cr) host material (∼35 kJ·mol⁻¹).[8a] This value is within the same range of value as those previously predicted for the interaction between various drugs and natural zeolites.[15] Both simulated drug geometry and strength of the drug-matrix interactions concur well with the experimental evidence pointed out by FTIR.

Kinetics of the Delivery. The MIL-53(Cr, Fe) materials were first compacted as cylindrical pieces leading to a small contraction of the pores, in agreement with the flexibility of the framework. The delivery of Ibuprofen was then performed using a simulated body fluid (SBF),[16] with inorganic composition similar to that of human plasma, at 37 °C under continuous stirring, while the delivered Ibuprofen concentration was determined by HPLC (high performance liquid chromatography) (Figures S8 and S9 in Supporting Information). Surprisingly, a very slow delivery, complete only after 3 weeks, is observed with clearly two steps in the process (Figure 5). Despite the slight changes of slope, the results were treated as a first approximation, as having a zero-order kinetics (Table 1 and Figure 5 and Figure S10 in the Supporting Information). One can note, however, some differences in the first step of the curves as a function of the nature of the metal. Whereas, for chromium, the delivery is close to linear, for iron, one observes a rapid beginning of delivery before a pseudo plateau and another increase of the delivery. The kinetics of delivery from MIL-53(Cr, Fe) were empirically adjusted with regression factors ≈0.99 to a zero-order kinetics ([Ibu] = Kt; Table 1 and Figures S5 and S10 in Supporting Information). XRPD performed before and after Ibuprofen release shows that their structures remain the same after the drug delivery and do not correspond, as expected, to the hydrated MIL-53lt form (Figures S3 and S4 in Supporting Information). This constance rules out any structural interpretation of the different behaviors of Cr and Fe at the beginning of the delivery. This invariance in the cell parameters might come from the use of an amine in the SBF organic base, which buffers the simulated body fluid (SBF). It might replace the Ibuprofen in the pores of MIL-53 during the release process. To confirm this, elemental analysis indicated the presence of 1% of nitrogen after the delivery (Table S3 in Supporting Information). A calcination at 275 °C under air atmosphere was then realized on the solid which led, back to

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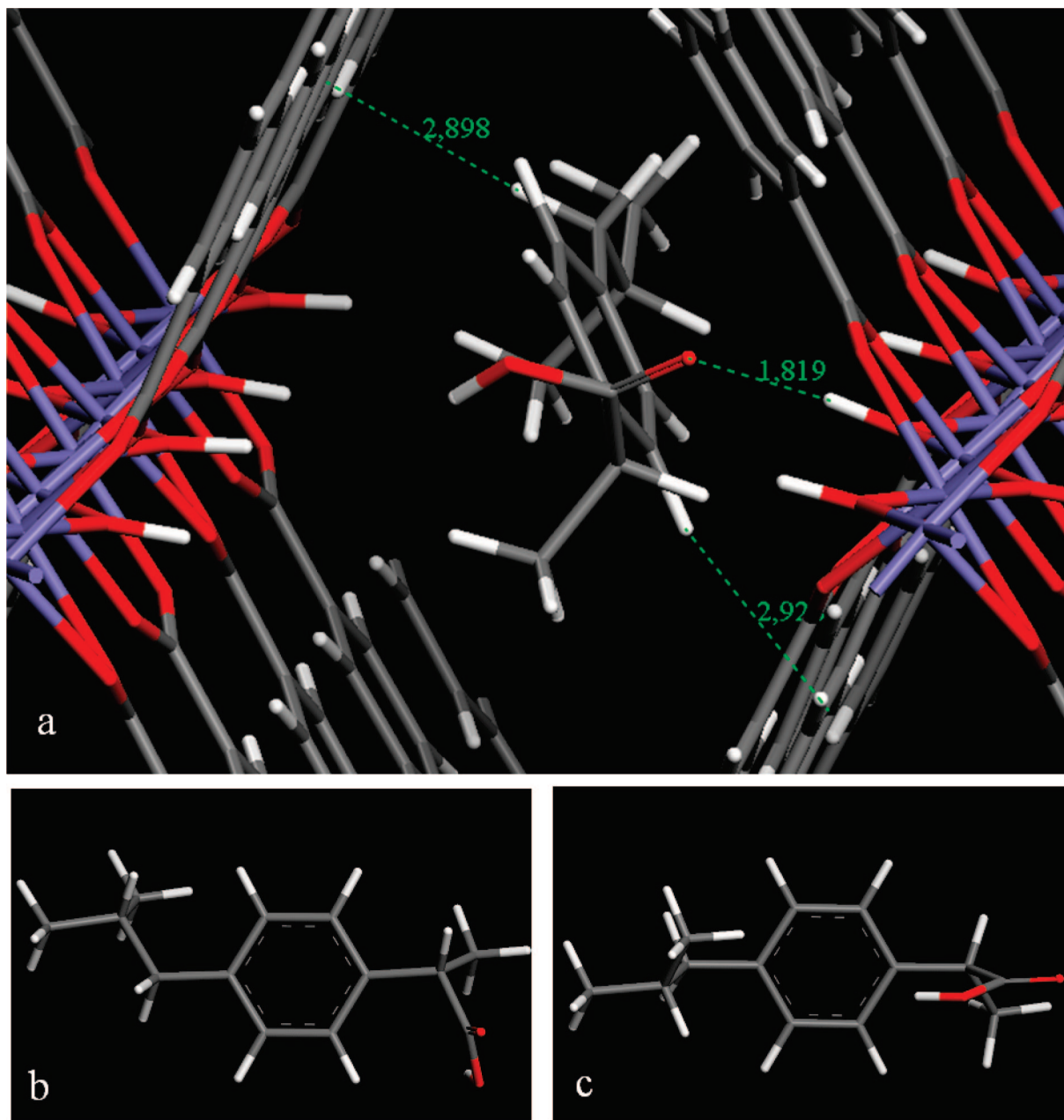
Figure 4. (a) Optimized arrangement of the Ibuprofen molecule in the MIL-53(Fe) material obtained from our DFT calculations. The distances are reported in angstroms, iron in blue, oxygen in red, carbon in gray, hydrogen in white. Structural arrangement of the molecule of Ibuprofen trapped in MIL-53(Fe) (b) compared to those obtained for the single molecule in the gas phase (c).

room temperature, to the hydrated MIL-53lt form (Figures S3 and S4 in Supporting Information).

After the drug delivery, no increase in pore volume is observed due to the adsorption of the ions and the organic base from the SBF medium. However, after the amine removal by calcination at 275 °C, almost 2/3 of the initial pore volume is recovered. The retention of ions (from SBF) inside the pores might explain this loss in pore volume.

Discussion

Some information can be summarized from the above characterizations: (i) Ibuprofen is adsorbed in MIL-53 solids after 3 days as a neutral molecule (see NMR); (ii) once Ibuprofen is inserted, its COOH groups and the OH groups of the framework strongly interact, as characterized simultaneously by the high temperature (260 °C) at which Ibuprofen leaves the pores and by FTIR and DFT observations; (iii) once inserted, NMR shows that the molecule has a small mobility within the pores; (iv) the nature of the metal can have some influence on the first steps of the delivery; and finally (v) unusually long times for delivery are observed. Compared to zeolites with similar sizes of micropores ($\varphi \sim 7.4$ Å), which afford similar capacities (15−20 wt %), their corresponding release times (7 days) are much shorter than those in MIL-53.[17] The same observation is made with mesoporous solids, pure or functionalized (2−7 days).[3a,b] This clearly shows an influence of the flexibility of MIL-53 on the time of release, without neglecting the presence of OH groups in the structure.

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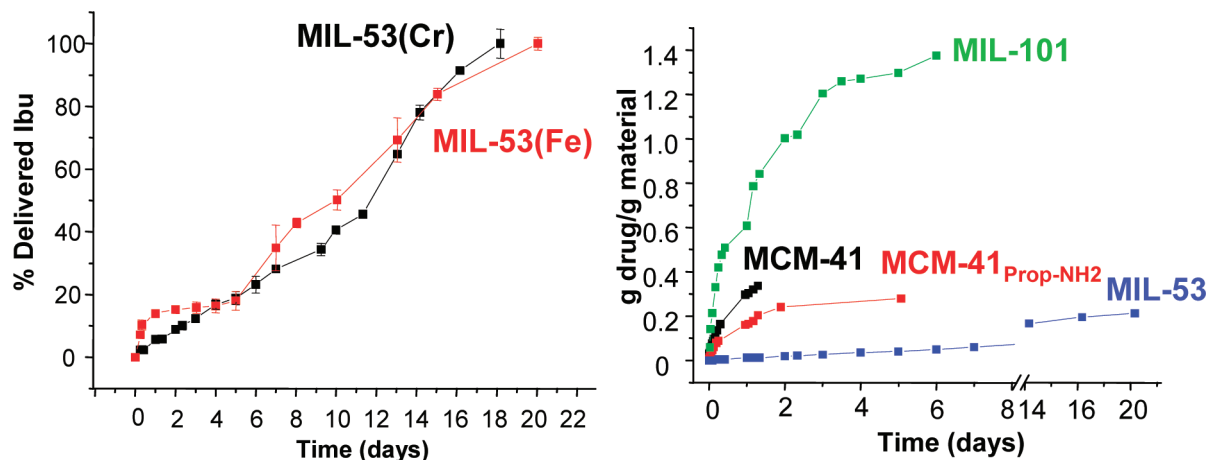
Figure 5. Ibuprofen delivery (left) from MIL-53(Cr) and MIL-53(Fe) materials (% Ibu − t); (right) from MIL-53 in comparison, MIL-101, MCM-41, and MCM-41$_{Pr-NH_2}$ (g Ibu/g solid − t).

How can one estimate the influence of the flexibility? It must be recalled that the maximum opening of the structure (observed with MIL-53(Cr)ht) is ca. 1500 Å^3. In the case of H_2O[9] and CO_2,[18] MIL-53(Cr) exhibits a contraction of the pore volume up to 45%. In the case of Ibuprofen, the pore contraction is less than 10%. This could be explained by the larger size of the drug molecule (∼5 ×10 Å). From this fact, one can suggest the specific behavior of flexible frameworks on the adsorption of species (gases, vapors, drugs, etc.), compared to rigid ones. They are adaptative and take, within the same topology, a configuration where the interactions between guest molecules and the framework are optimized while taking also into account the steric hindrance of the guest molecules and their number. If the latter increases due to a supplementary stimulus (increase of pressure for instance), the structure will open more. It is particularly the case for the two-step CO_2 adsorption:[17] at low adsorption (2 CO_2 per unit cell), the structure shrinks; at high pressure, the structure opens with 10 molecules inserted.

This adaptability might explain the long time of delivery. Indeed, due to its flexibility, MIL-53 can be considered as an intrinsically tailor-made container which fits with the geometrical and energetical characteristics of the guest and therefore enhances the confinement effects. If the latter are optimized, they will not favor rapid evacuation of the guests and therefore justify the long times for release.

However, such an argument does not explain the approximately zero-order kinetics. If it is the case, we can only observe a continuous decrease of the Ibuprofen loading with time. This implies the invariance of the local environment of the drug moieties within the pores during the whole delivery process. XRPD confirms this hypothesis since the patterns before and after the delivery are similar. It could be due to the exchange between the Ibuprofen molecules and the ions and organic amine from the SBF medium.

A kinetics model can be proposed since the matrix does not dissolve under the test conditions, and the release of Ibuprofen confined in the micropores is due to a gradual desorption from inside the pores, according to XRPD data. In these conditions, and assuming that the MIL-53 materials behave like a microporous membrane of monodimensional channels, a steady state should be reached at reasonably long times with the following boundary conditions: $C = C_0$ and $x = 0$ at $t = 0$ and $C = 0$; $x = l$ at $t \geq 0$, where C_0 is the initial concentration of Ibuprofen in the matrix and l is the thickness of the membrane with a value approximated to the particle size that contains the drug molecule.

In these conditions, it can be demonstrated that the solution of the Fick's second law[19] (eq 1) is the following:

$$\frac{dc}{dt} = D\frac{d^2C}{dx^2} \tag{1}$$

$$C = C_0\frac{x}{l} + \frac{2}{\pi}\sum_{n-1}^{\infty}\left(\frac{C_0}{n}\cos(n\pi)\cdot\sin\left(\frac{n\pi}{l}\right)\cdot e^{\frac{n^2\pi^2 D_t}{l^2}}\right) \tag{2}$$

where x is the position (length in meters) and D (m^2·s^{-1}) is the diffusion coefficient of Ibuprofen through the microporous system, which is assumed to be constant in its present approach. This equation can be solved, through the adequate integration procedure, for the cumulative released mass of Ibuprofen by surface unit, M (kg·m^{-2}), that leaves the material in a time t to give

$$M = \frac{DC_0}{l}t - \frac{lC_0}{6} - \frac{2lC_0}{\pi^2}\sum_{n-1}^{\infty}\frac{(-1)^n}{n^2}e^{\frac{n^2\pi^2 D_t}{l^2}} \tag{3}$$

when the time is long enough, this quantity can be approximated to

$$M = \frac{DC_0}{l}t - \frac{lC_0}{6} \tag{4}$$

which corresponds to a linear relationship $M = bt + a$ where $b = DC_0/l$ and $a = lC_0/6$.

The so-proposed model considers that the release needs a long time, depending on the material and the boundary conditions, to reach the stationary state and, therefore, to be able to be consistent with the previously mentioned approximations. In that case, the release profiles would have to display different kinetics: one of stabilization until the stationary state is reached, and a second one corresponding to a continuous delivery up to

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$C = 0$, that is, a total release. In Figure 5, the stabilization is reached at different periods for both materials (MIL-53-Cr in 10 days and MIL-53-Fe in 4 days), and these steps are either linear or exponential (or quadratic). The stationary state is clearly linear in both cases and seems to lead to negative values of the released mass at $t = 0$, in agreement with the fitting a parameter. The stabilization mechanism can be essentially due to the time needed to wet the solid since MIL-53 possesses both a polar subunit (metal octahedra) and a nonpolar part (aromatic rings) with a hydrophobic character. Thus, as we have previously described, MIL-53Fe and MIL-53Cr show a different breathing behavior. Even if the hydrated and Ibuprofen form is identical in both solids, MIL-53(Fe) stays closed unlike its Cr analogue in the dehydrated form, so we can suggest a different wetting kinetics based on the different breathing behavior. Thus, if the wetting is slower during the step of stabilization, the release will be presumably linear (in the case of the MIL-53(Cr)), and if it is faster, it will be exponential (in the case of MIL-53(Fe)). This is in total agreement with the empirical fitting of the curves in both stages (Table 1 and Figure S10 and Table S5 in Supporting Information). The regression factors are very close to 0.99, even if in some cases they are slightly below 0.99, we can use the fit as an empirical approximation (Table S5 in Supporting Information).

Finally, one could expect very long therapies using flexible MOF solids for drug delivery. Also, the possibility of having drug carriers with zero-order kinetics would represent an important progress since a unique administration could be provided. This would lead to a stable blood concentration, a minimization of the toxicity effects, as well as a decrease in patient discomfort. Moreover, the slow release will protect the drug from degradation processes by increasing its plasmatic half-life and bioavailability and therefore its efficiency.

Conclusion

This study reports for the first time that flexible porous metal-organic frameworks could be used as controlled delivery systems, with an unusual zero-order kinetics drug release which is a consequence of the flexibility of the framework which adapts its pore size to the dimensions of the drug to optimize drug-matrix interactions. Finally, the large variety of available flexible crystalline iron carboxylate solids (MIL-53, MIL-88 series, MIL-89) offers many possibilities to achieve an adequate controlled release of various pharmacological molecules. Among them, the MIL-88 series with pore sizes from 6 to 16 Å and breathing amplitudes between 85 and 230% in volume are particularly promising.

Supporting Information Available: Full data of synthesis method, Ibuprofen adsorption and delivery assays, as well as the optimization study of Ibuprofen incorporation and determination of Ibuprofen content by TGA, UV−vis spectroscopy, and elemental analysis and XRF. X-ray powder diffraction data, N_2 adsorption porosimetry, infrared spectroscopy, DFT calculations, HPLC and ^1H and ^{13}C NMR spectroscopy results. This material is available free of charge via the Internet at http://pubs.acs.org.

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