Investigating carrier degradation and drug release mechanisms of metal-organic framework nanoparticles

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Statement of Purpose:

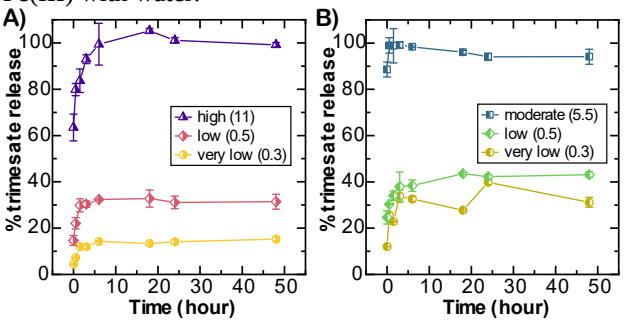
Controlled drug delivery promises optimal administration of the active substances to patients by attaching the drug to a designed carrier, which ideally can protect, transport, and release the drug at the desired space for the desired duration. For the drug carrier, metal-organic framework nanoparticles (nanoMOFs) have been recently investigated because of several strategic advantages for drug encapsulation, such as permanent porosity and tunable design. Among popular candidates like ZIF-8(Zn), MIL-100(Fe), and UiO-66(Zr), MIL-100(Fe) remains the most studied system, which has proven: high drug payload and encapsulation efficiency[1], biocompatibility, and biodegradability[2]. However, there is still debate about the degradation products of nanoMIL-100(Fe) and whether they can be safely removed from living bodies. It was reported that nanoMIL-100(Fe) degrades rapidly in phosphate-containing biological media without changing its size but forms a core-shell structure[3]. Recently, the aluminum analog nanoMIL-100(Al) was also proposed as a drug delivery system[4], and its specific interaction with phosphate-bearing molecules was also reported[5]. Curious about the degradation and erosion mechanisms of nanoMIL-100 materials, the present work studies the reaction mechanism of the aluminum- and iron-based nanoMIL-100 in a phosphate-containing medium.

Methods:

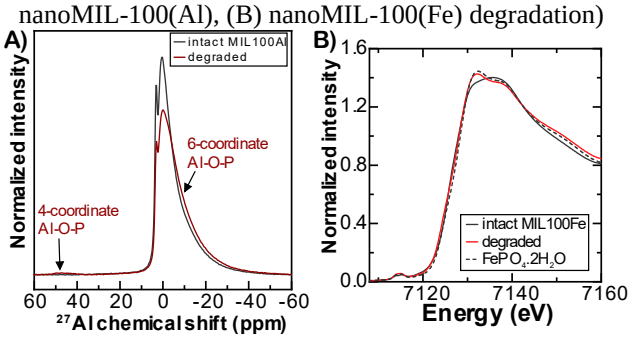
NanoMIL-100(Al) and nanoMIL-100(Fe) were synthesized by microwave synthesis. The synthesized nanoMOFs were characterized routinely by X-ray diffraction and N_2 adsorption to verify their crystallinity and porosity. To study the MOF degradation reaction, nanoMIL-100 was incubated in phosphate buffer saline (PBS) at pH 7.4 at 37oC and several phosphate-to-metal (P/M) molar ratios: 0.3, 0.5, 5.5, and 11. After a given time, the suspension in PBS was separated into degraded supernatant and pellet. Spectroscopic techniques, namely NMR, XPS, and XANES, were used to probe the change in nanoMOF's coordination structure upon its degradation. X-ray scattering and electron microscopy were used to monitor the size and morphological evolution of MIL-100 nanoparticles.

Results:

First, free trimesate was found in the degraded supernatant. The kinetics of trimesate release (Figure 1A, B) demonstrates the role of the P/M molar ratio. Second, the degraded MIL-100(Al)/MIL-100(Fe) pellet contained 6- and 4-coordinate aluminum phosphate/iron phosphate. The 6- and 4-aluminum phosphate was detected at -2 ppm and 48 ppm, respectively in ^{27}Al MAS NMR of the degraded nanoMIL-100(Al) (Figure 2A). The Fe K-edge XANES structure of iron phosphate was detected in the degraded nanoMIL-100(Fe) (Figure 2B). A molecular reaction mechanism between MIL-100 and phosphate is proposed. Principally, the MIL-100's native ligands are replaced with phosphate ions from PBS. Using the same strategy, we also showed that drug encapsulation and surface coating influence the nanoMIL-100 degradation as a function of the affinity between the drug/coating molecules and nanoMIL-100. Nevertheless, at the nanoscale, the degradation processes of these two MIL-100 analogs have distinctive behaviors due to different interactions between Al(III) / Fe(III) with water.



(Figure 1: Kinetics of trimesate release from (A) nanoMIL-100(Al), (B) nanoMIL-100(Fe) degradation)



(Figure 2: (A) ^{27}Al MAS NMR spectra of intact and degraded nanoMIL-100(Al), (B) Fe K-edge XANES spectra of intact and degraded nanoMIL-100(Fe))

References:

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