Supercritical CO_2 synthesis of CaSyr-1 BioMOF and its promising properties as drug delivery system

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1. Introduction

Metal-organic frameworks (MOFs) are crystalline materials constituted of metal centers and organic ligands that commonly exhibit highly porous networks with unique versatile chemistry.[1] This versatility, provided by the rigorous selection of their subunits, allows the optimization of their intrinsic properties for each scenario.[2] In biomedicine a variety of MOFs called biological MOFs (BioMOFs) have been developed with non-toxic and, sometimes, bioactive subunits.[3] In this field, they have been mostly proposed as nanocarriers of other bioactive compounds with the purpose of avoiding drug degradation before reaching the action target and, thus, performing a controlled release of it.[4] Nevertheless, one serious inconvenient in MOFs synthesis, regarding this application, is the usual necessity of employing toxic solvents, such as DMF, to induce the crystal growth of the framework. These solvents generally get trapped in the internal cavities of the MOF, being difficult to eliminate. Therefore, it is of major importance to develop green strategies to produce totally biocompatible BioMOFs.

The use of supercritical CO_2 ($scCO_2$) in MOFs preparation has been scarce and mainly limited to post-synthesis activation.[5] However, the capability of $scCO_2$ to solubilize many compounds, including some MOF precursors, indicates that $scCO_2$ could be a suitable media for the preparation of these materials as a green alternative.[6] In our group we have already proved this possibility by the successful preparation of different BioMOFs in an eco-friendly, facile and fast way.[7,8] Herein, we report the $scCO_2$ synthesis of a new BioMOF (CaSyr-1) constituted of calcium dication (Ca^{2+}) as metal node and syringate dianion (Syr^{-2}) as organic linker, both biologically active.[9,10] CaSyr-1 displays a highly porous crystalline structure with a stimuli-responsive nature, properties commonly sought in drug delivery systems.[11] As case study, it is tested for the encapsulation of the model drug Ibuprofen (Ibu), showing promising preliminary results.

2. Materials and Methods

Materials: For CaSyr-1 synthesis, the used reactants were H_2Syr (Sigma-Aldrich) and $Ca(acac)\cdot 2H_2O$, which was prepared by reacting acetylacetonate (acac, Sigma-Aldrich) with $Ca(OH)_2$ (Merck). For drug impregnation, the used active compound was Ibu (Sigma-Aldrich). The employed solvents were ethanol (EtOH, Scharlab) and $scCO_2$ (provided as compressed CO_2, 99.95 wt%, by Carburos Metálicos S.A.).

Methods: CaSyr-1 preparation was carried out in a high pressure vessel of 100 mL. The autoclave was charged with a 10 mL pyrex vial covered with filter paper containing 1 mmol of each reactant and 2 mL of EtOH (cosolvent) together with a small magnetic stir bar. Liquid CO_2 was flushed into the vessel at 6 MPa and then heated at 333 K. The pressure was increased up to 15 MPa by compressing CO_2 with a syringe pump and stirring was set at 500 rpm. These working conditions were maintained for a period of 48 h. After this time, the crude was washed with fresh $scCO_2$ twice by depressurization-pressurization (from 7 to 15 MPa). Finally, the reactor was completely depressurized and cooled down to room temperature. *(Note: for Ibu impregnation experiments, obtaining CaSyr-1(Ibu), the same procedure was followed but including 100 mg of Ibu in the vial).* In order to induce phase transformation from porous to non-porous material, 50 mg of CaSyr-1 were placed into a plastic vessel submitted to saturated HR for 24 h.

3. Results and discussion

CaSyr-1 was prepared following a green and facile $scCO_2$-based procedure and obtained as a crystalline nanopowder with an adequate particle size to exhibit great bioavailability.[12] The BioMOF, with formulae $CaSyr{\cdot}H_2O$, presents a highly porous 3D crystalline structure with two types of one-direction channel-like voids with a similarly large diameter, *ca.* 1.7 nm, but slightly different shape, *i.e.* elliptic and circular (**Fig. 1a inlet**). This porosity was experimentally confirmed by the analysis of N_2 adsorption-desorption isotherms, which indicate a predominant microporous character with a BET surface area of 750 m^2g^{-1} (**Fig. 2**). Some signs of framework flexibility could be noticed from the hysteretic shape of the isotherms, albeit further characterization should be performed to confirm this parameter.[13]

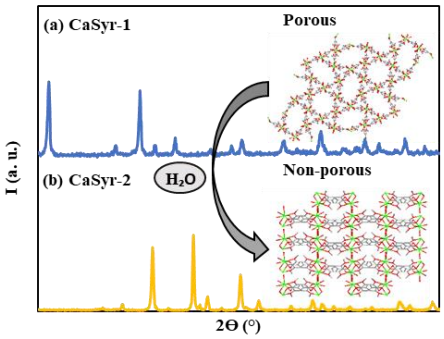

Figure 1. XRD pattern of (a) porous and (b) non-porous Ca-Syr, and their crystalline structures (inlets)

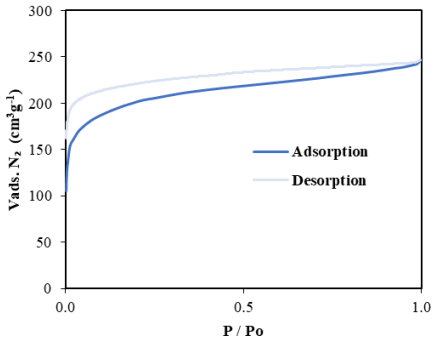

Figure 2. N_2 ads-des isotherm of porous Ca-Syr

Besides CaSyr-1, another coordination polymer (CP) containing the same building units, *i.e.* Ca^{2+} and Syr^{2-}, but with one extra H_2O in the coordination sphere, has been recently synthesized in our labs following a water-mediated approach (CaSyr-2). Unlike the other, it presents a 2D non-porous crystalline structure (**Fig. 1b inlet**). Knowing the existence of both forms, the transition of CaSyr-1 to CaSyr-2 was investigated in terms of hydration, see XRD patterns (**Fig. 1)**. Remarkably, it was observed that CaSyr-1 undergoes a solid transition to CaSyr-2 when submitted to high HR. This stimuli-responsive nature is of great importance in material science, but particularly relevant in systems involving host-guest molecular interactions.[11]

To squeeze its potential, CaSyr-1 was tested for encapsulating Ibu as a model drug, again, making use of $scCO_2$. The preliminary results show that Ibu successfully precipitates inside CaSyr-1 pores. On-going work is currently focused on studying CaSyr-1(ibu) phase transformation and the controlled release of the drug.

4. Conclusions

In this work, a $scCO_2$-based green method for the preparation of a new porous BioMOF is described. The bioavailability and biocompatibility of the material together with its hollow internal structure, with considerably large pores and likely flexibility, and the possibility to shift to a non-porous architecture, make it an ideal platform for the encapsulation of other active compounds in drug delivery systems.

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