NEW, POROUS METAL-ORGANIC FRAMEWORK AS POTENTIAL, BIOCOMPATIBLE DRUG DELIVERY SYSTEMS

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ABSTRACT

Metal-organic frameworks (MOFs) are complex structural materials synthesised form inorganic and organic constituents, most commonly via solvothermal method. Taking advantage of their properties such as large pore surface and volume together with the use of biofriendly constituents, we can design bioMOFs which can be used for drug delivery. To that effect a new porous bioMOF has been synthesised and optimized via solvothermal method using non-toxic solvent. This nano-bioMOF has a cubic crystalline structure that is stable up to 200°C. Constructed form zinc and ascorbic acid (vitamin C), this new bioMOF represents a great candidate for drug loading. With BET surface of 553 m^2/g and with pore windows of approximately 1 nm this bioMOF is suitable for loading smaller active pharmaceutical ingredients.

Keywords: metal-organic framework, biocompatible, zinc, ascorbic acid.

INTRODUCTION

Metal-organic frameworks (MOFs) are "*…coordination networks with organic ligands, containing potential voids.*" as stated by IUPAC recommendations [1]. MOFs have many impressive properties, but most outstanding of the features are high porosity (up to 6000 m^2/g) and really high surface to volume ratio. Because of these special features they offer many different applications, such as catalysis, separation, sensing and gas storage. Their tuneable structure and broad verity of pore shapes and sizes offer a certain advantage over related materials (zeolites and mesoporous silica) [2]. In 2006 MOFs attracted research interest form biology and medicine– namely they were proposed as drug delivery systems [3], contrast agents [4] and later in 2010 also as teranosis systems [5]. MOFs are deemed suitable for drug delivery because of several features. They have (i) large pore volumes and surfaces with the possibility of high drug loading, (ii) their internal pore surface and external surface can be functionalized, (iii) they offer a possibility of controlled drug release, (iv) when designing a MOF we can use bioactive constituents – making a so called bioMOF and (v) they can be biodegradable [6].

Definition of MOFs lives the choice of metal and linker to us, so in theory any metal and any organic molecule could be used in designing a MOF. However when designing a biocompatible MOF for the purpose of biological application, the choice of constituents is largely based upon the toxicity [2]. When choosing a metal for new bioMOF we consider metals that are endogenous, abundant and non-toxic ie. Fe, Mg, Zn, Ca; that have high LD_{50} values or we look for metals that have interesting properties (ie. Ag - antimicrobial activity; Mn – contrasting agent for MRI). For the bioactive linker we can choose from different groups of organic bio-molecules with abilities to coordinatively bind with metal cations, for example amino acids, peptides and proteins, nucleobases, porphyrins, saccharides, pharmaceutically active ingredients and other biologically active molecules[2].

Depending on desired administration route there are, in some cases, strict particle size requirements, especially in intravenous route where particles must be smaller than 200 nm in order to freely circulate without aggregation. Although classical solvothermal method can yield nanoMOFs and is a common method of choice we can also synthesise nanoMOFs with

reverse microemulsion, ultrasonic synthesis and microwave irradiation (or – MW solvothermal) [7]. The biggest problem that we face currently is the choice of a solvent which must be non-toxic or completely removed after synthesis. So when designing a new bioMOF or modifying the synthesis protocol for an already known MOF we can for example follow GlaxoSmithKline (GSK) solvent selection guide [8] which ranks solvents based on their environmental, health and safety impact. Once the synthesis yields some sort of a product we need to determine if it is a new MOF, known MOF or did we get an amorphous phase and need to adjust the synthesis protocol. First methods of choice for basic MOF characterization are powder X-ray diffraction (PXRD) and nitrogen (N_2) adsorption / desorption isotherms. After basic characterisation, additional characterization technique and protocols are performed in order to determine thermal and aqueous stability, crystal size and morphology as well as elemental composition and purity [9].

In this article we present newly designed bioMOF which constitutes of endogenous metal and hydrophilic vitamin as organic linker. Original synthesis and its optimization are done in a nontoxic solvent. Besides favourable constituents and bio-friendly synthesis new bioMOF also exhibits satisfactory BET surface area and pore volume to offer a possibility of drug loading.

EXPERIMENTAL

Chemicals and reagents: Zinc(II) acetate dehydrate ($Zn(CH_3COO)_2 \cdot 2H_2O$) and L-Ascorbic acid (ASC) were purchased from Sigma-Aldrich (Germany). Absolute ethanol (EtOH) was acquired from Carlo Erba (Italy).

Synthesis and optimization:

Zn-ASC-4 synthesis: 376, 752 or 1128 mg of $Zn(CH_3COO)_2 \cdot 2H_2O$ together with 300 or 600 mg of ASC and 10mL of EtOH were put inside a 23 mL Teflon ParrBomb (Parr Instrument Company, USA) and incubated for 24 h or 72 h at 100 °C or 120 °C in a Binder oven (Binder products, Germany). Tested ratios of Zn : ASC : EtOH were 1:1:100 ; 1:2:100 ; 2:1:100 and 3:1:100. Product was then recovered by filtration, washed with absolute EtOH and air dried.

Zn-ASC-4M synthesis: 752 mg of $Zn(CH_3COO)_2 \cdot 2H_2O$ together with 30mg of ASC and 10mL of EtOH were put inside a 100 mL Teflon vessel (Milestone, Italy) and incubated for 15, 30, 60 or 90 min at 120 °C in Milestone Touch Control microwave oven (Milestone, Italy), with the heating ramp of 5 min and power of 600W.

Post-synthetic activation: 100 mg of synthesised ZnASC-4 was dispersed in 100 mL of absolute EtOH and placed in an oil bath at 60 °C over night under reflux. Afterwards the product was carefully filtrated and dried on air.

Characterization: X-ray powder diffraction data was collected on PANalyticalX'pert PRO in 2theta range from 2 to 35 °. N_2 isothermal measurements were carried out on an IQ3 adsorber (Quantachrome). Specific surface area was calculated from BET theory, whereas pore size distribution was determined using NLDFT analysis. Scanning electron microscopy (SEM) was used to estimate the crystal sizes and morphology; coupled with energy dispersive X-ray spectroscopy (EDS) to get an insight in elemental composition and distribution. Thermal stability was examined by thermogravimetric analysis (TGA) on a Q5000 analyser (TA Instruments) and temperature-programmed XRD data collected on PANalyticalX'pert PRO diffractometer.

RESULTS AND DISCUSSION

Light beige to apricot coloured product, marked as a ZnASC4 in a form of a fine mate powder was produced in different stoichiometry starting ratios, times and temperatures using a classical solvothermal method. However the synthesis with the ratio Zn:ACS = 2:1 at 120

°C for 24 h had the highest yield of the product with superior crystallinity compared to others. This was determined by PXRD (Figure 1) and SEM (Figure 2), which in other samples beside the cubic crystallites of ZNASC4 exhibited undefined possibly amorphous phase. Crystals were estimated to be approximately 0.5 µm large and as no suitable single crystals were available, high-resolution XRD powder pattern was used to determine the crystal structure of ZnASC-4. Structure of new bio-MOF crystallizes in cubic symmetry (a = 20.881 Å) with the most probable chiral space group of I213.

TGA and HTK analysis in air flow show gradual degradation of the framework at 200 °C resulted in formation of ZnO residue at 250 °C as expected.

With the intent of using this bioMOF for biomedical administration, downsizing the crystals is necessary. So the optimization of original synthesis was done by switching the conventional heating for MW heating. The temperature staid the same, however the reaction time was significantly reduced to 1 h. Identity of the product was confirmed by PXRD (Figure 1), which also shows lower intensities and slightly broader peaks indicating the presence of nano-sized product. SEM analysis visually confirmed the presence of nano-crystals of estimated 20 nm (Figure 3).

N_2 sorption isotherm of ZnASC4 synthesized by conventional solvothermal method shows typical type I isotherm with the BET surface area value of 553 m^2/g and narrow pore size distribution showing the peak at 1 nm. Additional increase in uptake in the relative pressure range between 0.8 and 1 together with the profound hysteresis of the desorption branch can be ascribed to the substantial agglomeration of crystallites forming interparticle mesoporosity. ZnASC4M produced with the microwave solvothermal method shows significantly lower surface area (280 m^2/g) which can be a consequence of a lower crystallinity partially obstructing the accessibility of micropores.

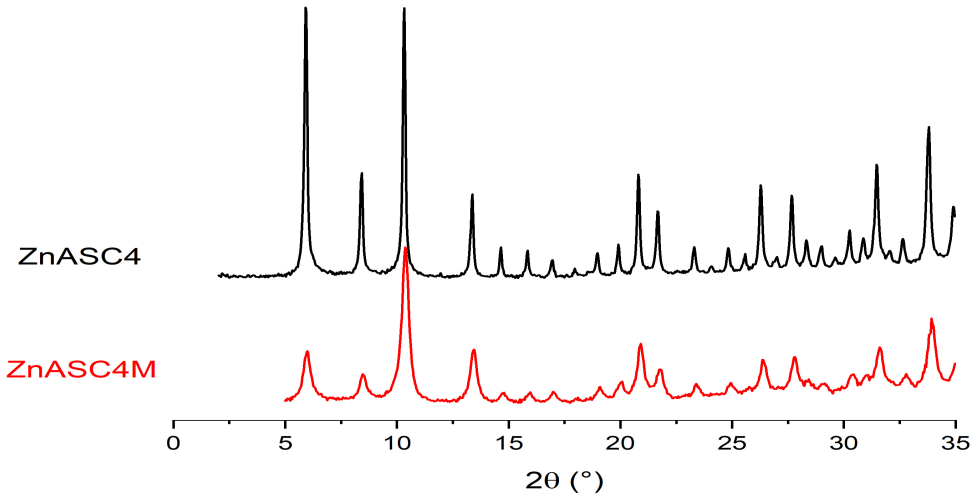
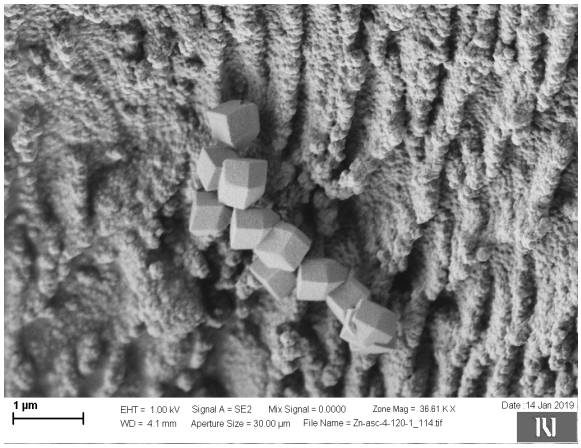


Figure 1. Comparison of X-ray diffraction patterns of ZnASC4 as synthesised,activated and ZnASC4M.



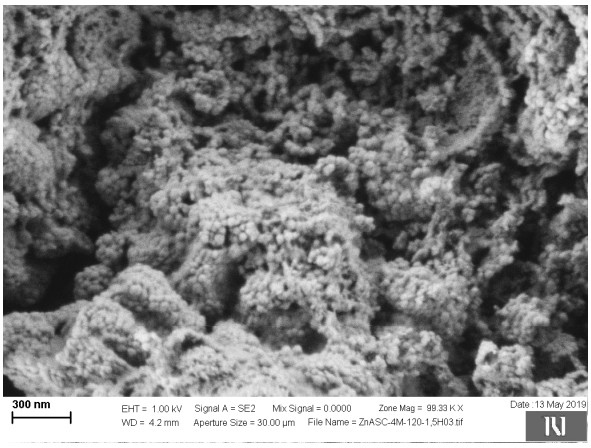


Figure 2.SEM photo of ZnASC4 crystals.Figure 3. Nano-MOF crystals of ZnASC-4M sample.

CONCLUSION

A new bioMOF material, denoted ZnASC4 was solvothermally synthesised based upon Zn^{2+} and ASC in EtOH, and its structure was (partially) characterized. BioMOF is stable up to 200 °C. Framework is porous with the BET surface of 553 m^2/g and with a pore windows of approximately 1nm and so suitable for drug loading of smaller pharmaceutical ingredients. Synthesis was optimized and successfully transferred from conventional oven to an MW oven and synthesis time was significantly reduced from 24h to 1h. Even though the synthesis in MW yields the same product the porosity / BET surface is not satisfactory so the synthesis still needs some optimization. Also further testing of aqueous and colloidal stability, as well as conformation of biocompatibility is needed to further confirm bioMOFs usability as drug delivery system.

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