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Cyclodextrin-based metal-organic frameworks particles as efficient carriers for lansoprazole: Study of morphology and chemical composition of individual particles

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ABSTRACT

Cyclodextrin-based metal-organic frameworks (CD-MOFs) represent an environment-friendly and biocompatible class of MOFs drawing increasing attention in drug delivery. Lansoprazole (LPZ) is a proton-pump inhibitor used to reduce the production of acid in the stomach and recently identified as an antitubercular prodrug. Herein, LPZ loaded CD-MOFs were successfully synthesized upon the assembly with γ-CD in the presence of K^+ ions using an optimized co-crystallization method. They were characterized in terms of morphology, size and crystallinity, showing almost perfect cubic morphologies with monodispersed size distributions. The crystalline particles, loaded or not with LPZ, have mean diameters of around 6 μm. The payloads reached 23.2 ± 2.1% (wt) which corresponds to a molar ratio of 1:1 between LPZ and γ-CD. It was demonstrated that even after two years storage, the incorporated drug inside the CD-MOFs maintained its spectroscopic characteristics. Molecular modelling provided a deeper insight into the interaction between the LPZ and CD-MOFs. Raman spectra of individual particles were recorded, confirming the formation of inclusion complexes within the tridimensional CD-MOF structures. Of note, it was found that each individual particle had the same chemical composition. The LPZ-loaded particles had remarkable homogeneity in terms of both drug loading and size. These results pave the way towards the use of CD-MOFs for drug delivery purposes.

1. Introduction

Metal Organic Frameworks (MOFs) have recently emerged as crystalline porous materials of interest for biomedical applications, with potential applications in drug delivery and imaging. Their high porosity, large surface areas, and versatility in terms of composition and functionalities make the MOFs particularly appealing for the incorporation of high drug payloads (Della Rocca et al., 2011; Horcajada et al., 2012; Li and Huo, 2015). Many efforts have been carried out to synthesize biocompatible MOFs using endogenous linkers or pharmaceutical acceptable excipients (McKinlay et al., 2010; Sontz et al., 2015; Su et al., 2015).

In particular, γ-cyclodextrin (γ-CD), a naturally available oligosaccharide enzymatically produced from starch, was used as a ligand to synthesize environment-friendly and biocompatible MOFs (Li et al., 2007). Advantageously, γ-CDs form inclusion complexes with a variety of drugs (Challa et al., 2005; Davis and Brewster, 2004). The γ-CD based metal-organic frameworks (CD-MOFs) were synthesized from γ-CD and K^+ ions employing a vapor diffusion method (Smaldone et al., 2010; Forgan et al., 2012; Furukawa et al., 2012;). It is widely recognized that size and polydispersity are crucial parameters in the design of drug delivery systems. In the originally reported synthesis (Smaldone et al., 2010), the size of CD-MOF crystals was around 200–400 μm. It was

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then discovered that the addition of cetyltrimethyl ammonium bromide (CTAB) in the preparation enabled the formation of smaller crystals (1–10 μm). Eventually, nanocrystals (200–300 nm) could be obtained by the addition of both CTAB and methanol during the synthesis procedure (Furukawa et al., 2012).

CD-MOFs with controlled sizes have shown their usefulness to incorporate molecules of interest (Michida et al., 2015; Moussa et al., 2016; Liu et al., 2016; Smaldone et al., 2010; Liu et al., 2017), including anti-inflammatory drugs (e.g., furbiprofen, fenbufen, ketoprofen and piroxicam), angiotensin converting enzyme inhibitors (e.g., captopril), food additives (e.g., curcumin, and sucralose), dyes (e.g., 4-phenylazophenol and rodamine B), and various pharmaceutical ingredients (e.g., salicylic acid, ferulic acid, and pseudolaric acid B). Drugs were loaded by impregnation in CD-MOFs (Moussa et al., 2016; Liu et al., 2016; Smaldone et al., 2010), but the obtained payloads were at best around 12.6% (wt) in the case of captopril (Liu et al., 2016), possibly because the small pore windows of the CD-MOFs limits drug penetration. The co-crystallization approach, where the drug was added during particle synthesis, enabled reaching higher payloads of 18.5% (wt) and 12.7% (wt) in the case of rhodamine B and ferulic acid, respectively (Smaldone et al., 2010).

Our aim here was to design CD-MOFs containing high payloads of lansoprazole (LPZ), a proton-pump inhibitor used to reduce the production of acid in the stomach and recently identified as an antitubercular prodrug targeting cytochrome bc1 (Rybniker et al., 2015). The administration of this drug is challenging because of its instability and strong tendency to crystallize. CD-MOFs were propose as carriers able to avoid drug degradation and crystallization over long-term storage. Crystalline LPZ-loaded CD-MOF with homogeneous sizes of around 6 μm were successfully synthesized *via* co-crystallization, showing cubic morphologies. The sizes are compatible with an oral or pulmonary administration as dry powder. LPZ payloads determined by both elemental analysis and HPLC, reached 23.2% (wt). To the best of our knowledge, these are the highest loadings reported so far with CD-MOFs.

Characterization studies on drug-loaded particles are currently performed on batches, but not on individual particles. By this way, no information can be drawn on the homogeneity of the particles in terms of drug incorporation. Indeed, each particle is unique in size, morphology and composition. For biomedical applications it is of outmost importance to gain insights on the quality of preparations, by analyzing individual particles to determine their size, morphology, crystallinity and chemical composition. To address this goal, Raman microscopy, which takes the advantages of both Raman spectroscopy and optical microscopy, was used here as a versatile powerful tool to record the morphologies and Raman spectra of individual MOF crystals.

2. Experimental

2.1. Materials and reagents

The chemical compounds, γ-CD, potassium hydroxide (KOH), cetyltrimethyl ammonium bromide (CTAB), isopropanol, trimethylamine, phosphoric acid, ethanol and methanol were purchased from Sinopharm Chemical Reagent Co. Ltd (France). Lansoprazole (LPZ) was provided by Zhuhai Rundu Co. Ltd (China). All chemicals were of analytical grade. Pure water used in all experiments was filtered (18.4 MΩ cm) by a Milli-Q system (Millipore, Milford, MA, USA).

2.2. Synthesis of CD-MOFs

CD-MOF crystals were synthesized by a modified methanol diffusion method as previously reported (Liu et al., 2016). The crystals were prepared by reacting γ-CD (0.125 mM) with 200 mM KOH in aqueous solution. The solution was then filtered through a 0.45 μm membrane into a glass vial followed by methanol diffusion at room temperature for several days until first crystals formed. CD-MOF obtained in this stage were named CD-MOF-1. To obtain monodispersed CD-MOF crystals, the supernatant was transferred into another glass tube with the addition of CTAB (8 mg mL^{-1}), which could trigger the rapid precipitation of CD-MOF crystals and then the suspension was incubated at room temperature for 3 h. The precipitate was harvested, washed thrice with isopropanol and finally dried at 50 °C overnight under vacuum to collect the CD-MOF crystals of about 5–10 μm, namely CD-MOF-2.

2.3. Synthesis of LPZ loaded CD-MOFs

LPZ-loaded CD-MOF crystals were synthesized in a similar way as empty CD-MOF. Briefly, the crystals were prepared by mixing LPZ (81.3 mM), γ-CD (0.125 mM) and KOH (200 mM) in 5.0 mL aqueous solution. The solution was filtered through a 0.45 μm organic filter membrane into a glass tube followed by methanol vapor diffusion for 24 h. The synthesized LPZ-loaded CD-MOF crystals were harvested by filtering through a 1.0 μm membrane and then washed with ethanol three times to remove the free drugs on the surface of the particles. After that, the drug loaded particles were dried at 50 °C under vacuum overnight. The LPZ loaded CD-MOF particles obtained in this stage were named LPZ/CD-MOF-1.

The supernatant was transferred into a new tube with the addition of CTAB (8 mg/mL) and incubated at room temperature for 3 h. The formed LPZ loaded CD-MOF crystals, namely LPZ/CD-MOF-2, were washed thrice with ethanol and dried at 50 °C overnight under vacuum.

The CD-MOFs loaded or not with LPZ were stored at room temperature in closed vials up to two years.

2.4. Characterization of CD-MOF crystals with or without LPZ

Morphological characterization of CD-MOF crystals with or without LPZ was conducted by SEM (S-3400N, Hitachi) and Raman microscopy (Morphologi G3-ID, Malvern®, Orsay). For SEM investigations, the particles were immobilized with an adhesive tape on a metal stub and then coated with gold. For Raman microscopy, the particles were spread on a slide and optical images of more than 2500 individual particles were captured automatically. Statistical analysis of sizes and morphologies was carried out using Morphologi software.

Crystallinity of the samples was characterized by X-ray powder diffraction (XRPD) analysis. Diffraction patterns of the samples were detected on an advance diffractometer (Bruker D8, Bruker, Germany). The detection was performed at ambient temperature, with tube current of 40 mA. Monochromatized CuKα radiation was used to irradiate the samples. The diffraction data was collected at a 2θ angle range of 3–40° with the stepwise scan mode of 8°/min on a diffractometer (X/Pert Pro 3040/60, PANalytical, Holland).

Chemical composition of individual CD-MOF crystals with or without LPZ were characterized by Raman microscopy. Raman spectra were obtained from 100 to 1900 cm^{-1}. As control, Raman spectrum of LPZ powder was also performed.

Drug payload is defined as the weight percentage of drug in the drug-loaded CD-MOF and was calculated using Eq. (1):

$$Payload\ (\%) = \frac{Encapsulated\ Drug\ (mg)}{Drug\ loaded\ CD-MOF\ (mg)} \times 100 \quad (1)$$