

DRUG DELIVERY SYSTEM FOR ARTEMISININ

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Abstract: Metal-organic frameworks (MOFs) are promising platform for drug delivery because of the high drug loading capacity, biodegradability, and function versatility. The study aims to develop a simple system of encapsulating important drugs. The paper describes the facile synthesis of the novel three-component metal-organic framework (MOF) involving Zn (II) ions and simple diacid ligands. Characterization of the novel MOF using IR, Elemental analysis, SEM, and EDX showed the metal and component ligands forming a three-dimensional framework with a porous surface. The novel MOF developed in this study was tested for its ability to encapsulate drugs as a potential drug delivery system. Encapsulation studies using Artemisinin, which is a medicine used for anti-malarial and anti-cancer treatment, reveal successful encapsulation as revealed by fluorescence microscopy, SEM, and EDX. The porous surface of the MOF, allows non-covalent interaction with the incoming drug and fits into the cavity via H-bonding and adsorption allowing the encapsulation of the drug. This new MOF from simple materials and prepared using simple process opens an avenue for new drug delivery system.

Keywords: *Metal organic framework, drug delivery, encapsulation studies, Artemisinin*

1. INTRODUCTION

Most drug delivery systems are based on organic polymers or inorganic porous solids (Horcajada, 2010). However, these materials have been shown to have poor bioavailability and slow pharmacokinetics in the body (Hrkach, 2008) sacrificing the efficacy of the drug. This research explores the hybrid porous solids consisting of a metal connecting points and organic bridging ligands or otherwise known as metal-organic frameworks (MOFs). MOFs are good drug-delivery materials due to its tunable pore size, high drug loadings, biodegradability, and function versatility (Huxford, 2010; Keskin, 2011). To date, most MOFs being explored are based on Co, Ni and Cr. However, these metals are relatively toxic (Horcajada, 2010). This work explores the non-toxic metals in preparing the MOF: iron (III) ($LD_{50}(\text{Fe}) = 30\text{g kg}^{-1}$) and zinc (II) ($LD_{50}(\text{Zn})=0.011\text{g kg}^{-1}$). Moreover simple diacids were used as bridging ligands: fumaric acid ($LD_{50}=10.7\text{g kg}^{-1}$) and oxalic acid ($LD_{50}= 0.375\text{ g kg}^{-1}$) ligands (Sheftel, 2000). Their non-toxic nature, porous morphology, and nanoparticle size make them promising drug delivery systems. Their efficiency as drug carriers was tested with the antimalarial and anticancer drug (Artemisinin (ART)) ($LD_{50}(\text{ART}) = 0.30\text{g kg}^{-1}$) (Nontprasert, 2000).

2. METHODOLOGY

The synthesis of MOF was performed in ethanol at room temperature via precipitation polymerization using zinc nitrate, fumaric acid and oxalic acid. The powdery white precipitates observed in the solution were filtered, washed with ethanol and oven dried.

The Artemisinin encapsulation was performed by mixing 100mg of the dehydrated MOF powder material in a 10ml solution of ethyl acetate containing 300mg of Artemisinin for 3 days. The white precipitates were filtered and washed with ethanol and oven dried.

Conversion of Artemisinin to a UV-active compound was performed by adding 0.20% NaOH into an acetonitrile solution of Artemisinin followed by at 45°C for 30 minutes (Zeng, 1983). Similar process was done to encapsulate the Artemisinin derivative.

3. RESULTS AND DISCUSSION

The combination of the three-component MOF (zinc, oxalic acid and fumaric acid) is unprecedented. The new MOF is insoluble in common organic solvents and does not melt below 300°C making the full characterization very challenging. To provide an insight regarding its structure, the FT-IR spectra of the oven-dried MOF shows OH stretching at 3392cm⁻¹ (*strong, broad*). The sharp tip of the peak suggests less extensive H-bonding indicating that most -COOH is coordinated to the metal. A broad strong peak at 1633cm⁻¹ is attributed to C=C absorption confirming the presence of the free C=C fumaric acid in the MOF. Since the zinc (II) metal is known to show no interaction with C=C (Rappoport, 2006) the MOF coordination should have formed via the COOH moieties. A noticeable shoulder at around 1700cm⁻¹ refers to C=O peaks confirming the presence of carboxylic acid (Figure 1).

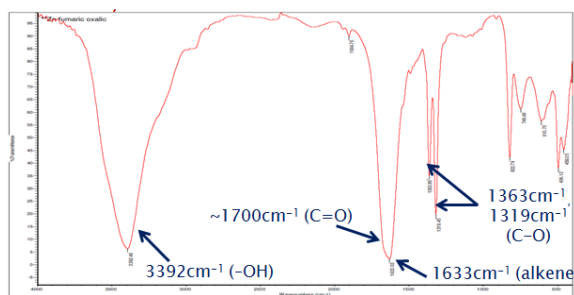


Figure 1 FT-IR spectra of the porous Zinc-fumaric-oxalic MOF

The powder XRD analysis of the MOF showed that it is only less than 80% similar to the known zinc oxalate hydrate indicating that the fumaric acid must have played a role in the formation of the MOF. Moreover, a strong 2θ peak at 23.5 is unique only to the MOF which cannot be observed for zinc oxalate.

The CHNS elemental analysis shows the presence of carbon and hydrogen. The EDX showed similar percentage of C. Moreover, EDX reveals the presence of O and Zn. Elemental analysis of MOF-Artemisinin is characterized by an increase in the %C and %H, relative to the bare MOF suggestive of Artemisinin encapsulation (Figure 2).

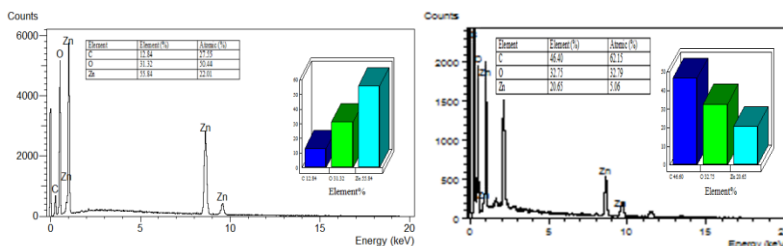


Figure 2 EDX spectrum of MOF (left) and MOF-Artemisinin (right)

The SEM analyses of MOF-Artemisinin, and MOF-artemisinin derivative indicate a more inflated morphology as compared to the bare MOF suggestive of the filling in of the drug in the porous MOF as shown in Figure 3. When viewed under UV light in the fluorescence microscope the bare MOF and MOF-Artemisinin revealed no fluorescence. However when a derivative of Artemisinin which is a UV-active compound was prepared and encapsulated into the MOF, fluorescence microscopy showed that the sample fluoresces when viewed under the UV-light. The measured UV wavelength of 260nm confirms the presence of the Artemisinin derivative. These results suggest the successful encapsulation of Artemisinin.

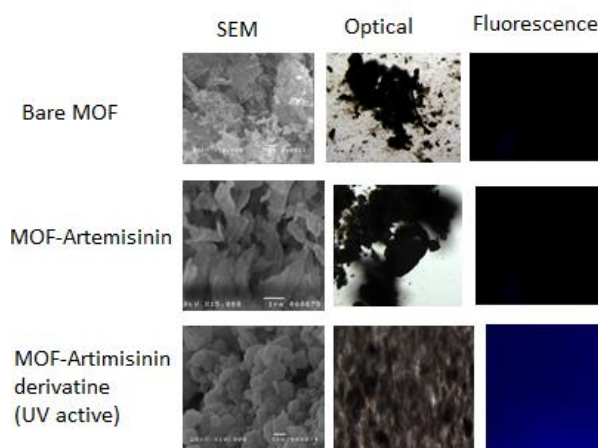


Figure 3 SEM , optical and Fluorescence images of MOF, MOF-Artemisinin and MOF-Artemisinin derivative

The results in this study suggest that the more likely encapsulation scheme involves adsorption of the drug to the MOF via H-bonding. The porous surface of the MOF, allows non-covalent interaction with the incoming drug and fits into the cavity via H-bonding and adsorption allowing the encapsulation of the drug. This new MOF from simple materials and prepared using simple process opens an avenue for new drug delivery system. Isotherm studies and drug release investigations are underway.

CONCLUSION

The study described a novel MOF system that shows promise in drug delivery application from biologically compatible and readily available compounds: Zinc (II), fumaric acid, and oxalic acid. The three component reaction between zinc, oxalic acid and fumaric acid to give the new MOF is unprecedented and showed great promise in the drug delivery system due to its porous nature. Characterization of the novel MOF was done using IR, Elemental analysis, Powder XRD, SEM, and EDX. Successful encapsulation of Artemisinin into the MOF was demonstrated.

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