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MIL-53(Fe), MIL-101, and SBA-15 porous materials: Potential platforms for drug delivery

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ABSTRACT

Conventional drug administration suffers from several drawbacks, including a lack of specificity for diseased tissue, the necessity of large and frequent doses, and adverse side effects. Great effort is currently being devoted to developing nanoparticle-based therapeutics capable of prolonging drug administration and providing better control. Here we demonstrate the use of flexible microporous MIL-53(Fe) and mesoporous MIL-101 and SBA-15 as matrices for the adsorption and in vitro drug delivery of acetaminophen, progesterone, and stavudine. A drug loading of 20 wt.% was achieved for each of the nanomaterials using an incipient wetness impregnation procedure. BET, DSC, and XRPD analyses indicated that the entire loaded amount of each of the model drugs had successfully been incorporated within the mesoporous channels of both MIL-101 and SBA-15. DSC analysis evidenced that a portion of each of the model drugs had deposited onto the outer surface of MIL-53(Fe) particles; however, the portion of each drug that had incorporated within the microporous channels was slowly delivered in a diffusion-controlled process, which occurred over a period of up to six days for acetaminophen. These results demonstrate the unique ability of MIL-53(Fe) to adapt its porosity and optimize drug–matrix interactions. Owing to its larger pore diameters and weaker host–guest interactions, MIL-101 release times were shorter, yet still prolonged, as evidenced by the complete release of stavudine after five days. Complete release of each of the drugs from SBA-15 occurred very quickly as a result of rapid drug dissolution and diffusion out of the mesopores.

1. Introduction

Porous materials have applications in a variety of practical fields, including chemical, optics, electronics, environmental/energy, medical, and biotechnology. These applications are attributed to their regular pore structures and high surface areas, which are useful for material adsorption, sensing, removal, storage, and release [1]. These last two properties give these materials the unique ability to be used as drug delivery systems (DDSs) to treat diseases. The shortcomings of conventional therapeutics can be alleviated by stabilizing drug plasmatic levels through a controlled release rate. Drug dosages can be reduced, thus increasing the efficacy and decreasing the toxicity of conventional drugs. In consideration of this, as well as with the fact that the development of new bioactive compounds is a time-consuming, complex and costly process, researchers have taken an interest in developing nanoparticle-based therapeutics in recent years [2]. Polymeric nanoparticles, micelles, liposomes, and microporous zeolites have already been extensively researched to this end; however, results have been unsatisfactory. Organic systems, such as biocompatible dendritic macromolecules or polymers, can be encapsulated with a wide array of drugs; however, in the absence of a well-defined porosity they lack a controlled release [3].

Currently, metal–organic frameworks (MOFs) have gained attention in this field, as they have been found to exhibit many desirable characteristics as drug carriers. Compared to prior unsuccessful drug carrier systems, MOFs offer several advantages. Their structures are highly tunable, which can be accomplished through a change of the metal and/or organic linker to effectively tune the pore size, structure and chemical properties. The high surface area of MOFs allows for the potential to achieve large drug loadings, whereas large pore sizes enable a wide range of pharmaceuticals to be encapsulated [4]. Their frameworks can even be designed to have a high structural flexibility and robustness, resulting in the ability of certain flexible MOFs to adapt their pores to accommodate the shape and size of organic molecules [5,6]. Each of these properties enables MOFs to achieve both a high drug loading and a controlled release of therapeutic agents to targeted areas of the body [7]. For example, the hydrated forms of MIL-53(Al, Cr) solids exhibit a reversible pore opening which involves atomic displacements by 0.52 nm upon dehydration, corresponding to an increase in pore volume up to 45%. Certain flexible MOFs have recently been shown to adapt the cell volumes of their structures by 50–230% without any noticeable change to their structural integrities [6].

MIL-53(Fe) was previously used as a matrix for the adsorption and in vitro delivery of ibuprofen. Horcajada et al. [6] showed that MIL-

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53(Fe) adsorbs 0.21 g ibuprofen/g MOF and has a very slow and complete delivery of ibuprofen in simulated body fluid at 37 °C over a three week period with an unusual zero-order kinetics drug release. They attributed this slow release to the flexibility of the framework, which allows it to maximize bonding interactions while still minimizing steric hindrance.

However, the application of microporous (pore diameters ≤2 nm) MOFs such as MIL-53(Fe) as DDSs is limited by their small pore sizes, and the choice of incorporated species is restricted to relatively small drug molecules, such as ibuprofen. Mesoporous materials (pore diameters between 2 and 50 nm) are more useful, because larger drug molecules can be accommodated, and their functionalities within the mesopores can be preserved [8]. Ferey and co-workers [3] demonstrated drug delivery with mesoporous MOFs, MIL-100 and MIL-101, which proved suitable due to their well-defined, ordered porosity. MIL-101 has a high Langmuir surface area of 5500 m^2/g, large mesoporous cages (~2.9 and 3.4 nm), and large window openings of 1.2 nm and 1.6 nm for the pentagonal and hexagonal windows, respectively. The researchers utilized these properties to store an unprecedented 1.4 g of ibuprofen per gram of MOF. The complete release of Ibuprofen was achieved under physiological conditions after six days. As evidenced by X-ray powder diffraction (XRPD), even at these high loadings there was no apparent loss of crystallinity or decomposition of the framework structure. These sustained release times and high drug loadings make the MIL family an attractive candidate for storage and controlled release of biologically important molecules.

The aim in this study was to evaluate to what extent reported sustained release times and high drug loadings were applicable to a series of three compounds with a high degree of physicochemical diversity. The drug loading and release behavior of acetaminophen, stavudine and progesterone encapsulated in either MIL-53(Fe), MIL-101, or a silica-based ordered mesoporous material (SMM), SBA-15 were evaluated. SMMs are characterized by their homogeneous and ordered pore networks, mechanical strength, thermal and pH stability, biocompatibility and silanol-containing surfaces that can be functionalized to allow for a better control over drug delivery [9,10]. SBA-15 consists of a hexagonally-ordered array of tunable pores which can range in diameter from 5 to 30 nm. It also has a high surface area ranging from 600 to 1000 m^2/g, and a large pore volume ranging from 0.8 to 1.2 cm^3/g [11]. These properties enable drug loadings upwards of 50 wt.% [12]. The structure of MIL-53(Fe) is composed of parallel trans corner-sharing iron(III) octahedral chains, each of which are cross-linked by 1,4-benzenedicarboxylate (BDC) anions to form a one-dimensional lozenge-shaped pore channel system. As previously mentioned, MIL-53(Fe) only opens its pores in the presence of guest molecules; therefore, unlike MIL-101 it does not have a high surface area. MIL-53 has the formula $M^{III}(OH)[(O_2C–C_6H_4–CO_2)] \cdot H_2O$ (where M = Al^{3+}, Cr^{3+} or Fe^{3+}) with pores of free diameter close to 1.3 nm [6]. MIL-101 is built up from trimers of chromium octahedra, which are also cross-linked by BDC, and has the formula $Cr_3OX(H_2O)_2[(O_2C)–C_6H_4–(CO_2)]_3 \cdot nH_2O$ (where X = F,OH and *n* is ~25) [13].

In this study we used an incipient wetness impregnation procedure to load each of the materials with a targeted drug loading of 20 wt.%. This target was chosen based on previous findings in which MIL-53(Fe) achieved a maximum drug loading of 20 wt.% for ibuprofen [5]. This incipient wetness process has previously been used to fill the mesopores of SMMs with a precise drug loading target; however, this procedure has not yet been reported for MOFs [11,14,15]. This is a more convenient method than the conventional loading procedure, which involves adsorption from an organic solution followed by cumbersome and time-consuming equilibration and filtration steps to recover the loaded carrier particles [14]. The loaded materials in this study were evaluated for their release profiles under simulated physiological conditions in phosphate buffered saline (PBS).

2. Experimental section

2.1. Model drugs

Three drugs were selected based on their diverse physicochemical properties, in order to obtain a test series with a high degree of diversity (Table 1). Acetaminophen is an analgesic which distributes rapidly and evenly throughout most tissues. Like stavudine, it is orally administered, and has a bioavailability ranging from 70 to 90% and a plasma half-life ranging from 1.9 to 2.5 h [16]. Stavudine is a nucleoside reverse transcriptase inhibitor (NRTI) used for the treatment of human immunodeficiency virus (HIV). It was approved for use by the Food and Drug Administration (FDA) in 1994. Seven NRTIs have been approved for use, but in general they have limited stability and poor bioavailability. As a NRTI, stavudine has a reasonably high bioavailability of about 80%. However, its half-life in systemic circulation is about 1 to 1.6 h, which necessitates frequent doses and results in severe dose-dependent side effects [17]. Progesterone is a steroid hormone belonging to the progestogen class that naturally occurs in both males and females. It is administered to individuals with a long-term decline of natural levels in the body, as well as to patients with acute situations. Like all steroid hormones it is hydrophobic; therefore, when taken orally it has a poor bioavailability and a half-life upwards of 50 h [18]. The dimensions of each drug were determined using ChemDraw. Acetaminophen (≈0.82 × 0.49 nm), progesterone (≈1.12 × 0.58 nm), and stavudine (≈0.85 × 0.58 nm) were all determined to have favorable dimensions for incorporation within the pores of each nanomaterial. Acetaminophen was purchased from Sigma-Aldrich (St. Louis, MO), progesterone was purchased from Calbiochem (La Jolla, CA), and stavudine was generously donated by Apotex PharmaChem Inc. (Brantford, ON).

2.2. Synthesis of materials

MIL-53(Fe) was synthesized with the same batch composition reported by Horcajada et al. [5] from a mixture of ferric chloride hexahydrate ($FeCl_36H_2O$, Caledon, 97.0–102.0%), 1,4-benzenedicarboxylic acid (H_2BDC, Alfa Aesar, ≥98%), and *N,N*-dimethylformamide (DMF, Caledon, ≥99.8%). All of the chemicals were used as purchased without any further purification. MIL-53(Fe) was synthesized by the same ultrasonic irradiation method that we previously reported, which was shown to be a highly efficient, rapid and low cost alternative to conventional MOF synthesis procedures [19]. The reaction mixture was prepared in a 50 mL glass beaker by dissolving 1.35 g of $FeCl_36H_2O$ and 0.830 g of H_2BDC in 25 mL of DMF. The beaker was placed in the probe of an ultrasonic generator (VCX 500, Sonics & Materials, Inc., Newtown, CT) and subjected to ultrasonic irradiation for 10 min at 70% of the maximum power; the temperature was not controlled. The as-synthesized product was prepared by centrifugation, DMF washing, and overnight drying. Prior to drug loading, the as-synthesized sample was subjected to three activation steps. To remove DMF from the pores the powder was heated for 24 h at 150 °C in an oven (DKN 400, Yamato Scientific America, Inc., Santa Clara, CA) and cooled down to room temperature. To remove traces of DMF, the powder was then stirred in a large volume of deionized water and filtered. Finally, the powder was dehydrated in the oven at 150 °C for 24 h to remove water from the pores. This synthesis technique produced small and homogeneous MIL-53(Fe) crystals, which is an essential feature of DDSs.

MIL-101 was synthesized hydrothermally according to procedures previously reported [3,13] from a mixture of chromic nitrate nonahydrate ($Cr(NO_3)_39H_2O$, Caledon, ≥98.0%), 1,4-benzenedicarboxylic acid (H_2BDC, Alfa Aesar, ≥98.0%), hydrofluoric acid (HF, EMD Chemicals Inc.), and H_2O. A solution containing 1.2 g of $Cr(NO_3)_39H_2O$, 0.492 g of H_2BDC, 0.1 mL of HF (52% in water), and 14.4 mL of H_2O was introduced into a 25 mL Teflon liner. The mixture was placed in a steel autoclave and